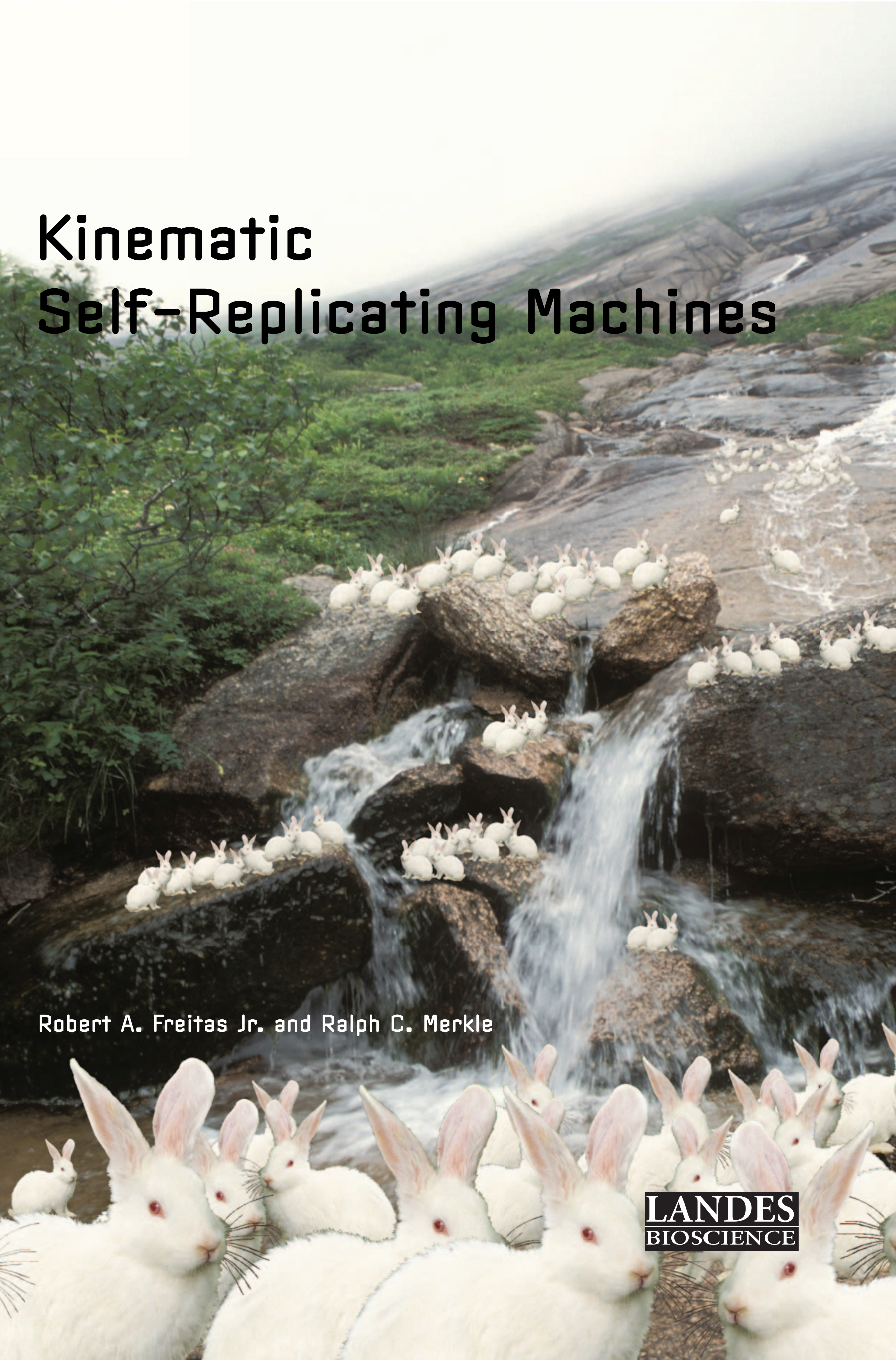


Kinematic Self-Replicating Machines

Robert A. Freitas Jr. and Ralph C. Merkle

LANDES
BIOSCIENCE

Kinematic
Self-Replicating Machines

Kinematic Self-Replicating Machines

Robert A. Freitas Jr.
Senior Research Fellow
Institute for Molecular Manufacturing

Ralph C. Merkle
Distinguished Professor of Computer Sciences
Georgia Institute of Technology

LANDES BIOSCIENCE/EUREKAH.COM
GEORGETOWN, TEXAS
U.S.A.

KINEMATIC SELF-REPLICATING MACHINES

LANDES BIOSCIENCE
Georgetown, Texas, U.S.A.

Copyright © 2004 Robert A. Freitas Jr. and Ralph C. Merkle.

All rights reserved.
No part of this book may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.
Printed in the U.S.A.

Please address all inquiries to the Publishers:
Landes Bioscience, 810 South Church Street, Georgetown, Texas, U.S.A. 78626
Phone: 512.863.7762; FAX: 512.863.0081

ISBN: 1-57059-690-5

Library of Congress Cataloging-in-Publication Data

While the authors, editors and publisher believe that drug selection and dosage and the specifications and usage of equipment and devices, as set forth in this book, are in accord with current recommendations and practice at the time of publication, they make no warranty, expressed or implied, with respect to material described in this book. In view of the ongoing research, equipment development, changes in governmental regulations and the rapid accumulation of information relating to the biomedical sciences, the reader is urged to carefully review and evaluate the information provided herein.

To all the replicators
we’ve known and loved

CONTENTS

Table of Contents vii
List of Figures xi
List of Tables xv

Preface and Achnowledgements xvii

Chapter 1. The Concept of Self-Replicating Machines 1

Chapter 2. Classical Theory of Machine Replication 5

2.1 Von Neumann's Contributions 5
    2.1.1 A Logical Organization of Self-Replication 6
    2.1.2 The Kinematic Model of Machine Replication 7
    2.1.3 The Cellular Automaton (CA) Model of Machine Replication 8
    2.1.4 Limitations of von Neumann's Cellular Automaton Model 10
    2.1.5 Design for Nonevolvability 10
2.2 Subsequent Work on Computational Models of Self-Replication 11
    2.2.1 Cellular Automata Models of Self-Replication 11
    2.2.2 Computational Modeling with Continuous Space and Virtual Physics 14
2.3 Alternative Models of Machine Replication 15
    2.3.1 Simplified von Neumann Automaton Replication 15
    2.3.2 Von Neumann Automaton Replication with Diversification 15
    2.3.3 Thatcher's Variant: Inferring Structure 15
    2.3.4 Replication by Component Analysis 16
    2.3.5 Machine Replication without Description 16
    2.3.6 Nonautonomous Machine Replication 17
    2.3.7 Embodied Evolution: Algorithmic Replication 18

Chapter 3. Macroscale Kinematic Machine Replicators 19

3.1 Moore Artificial Living Plants (1956) 19
3.2 Browning Unnatural Living State (1956, 1978) 20
3.3 Penrose Block Replicators (1957-1962) 21
3.4 Jacobson Locomotive Toy Train Replicator (1958) 23
3.5 Morowitz Floating Electromechanical Replicator (1959) 24
3.6 Dyson Terraforming Replicators (1970, 1979) 24
3.7 Self-Replicating Automated Industrial Factory (1973-present) 25
3.8 Macroscale Kinematic Cellular Automata (1975-present) 28
3.9 Space Manufacturing Systems with Bootstrapping (1977-present) 35
3.10 Taylor Santa Claus Machine (1978) 37
3.11 Freitas Interstellar Probe Replicator (1979-1980) 38
3.12 Bradley Self-Replicating Teleoperated Machine Shop (1980) 40
3.13 NASA Summer Study on Self-Replicating Systems (1980-1982) 42
    3.13.1 NASA Robot Replication Feasibility Demonstration 45
    3.13.2 Self-Replicating Lunar Factories 46
        3.13.2.1 Von Tiesenhausen Unit Replication System 46
        3.13.2.2 Freitas Factory Replication System 49
3.14 Freitas Atomic Separator Replicator (1981) 52
3.15 Lackner-Wendt Auxon Replicators (1995) 53
3.16 The Collins Patents on Reproductive Mechanics (1997-1998) 54
3.17 Lohn Electromechanical Replicators (1998) 58
3.18 Moses Self-Replicating Construction Machine (1999-2001) 60
3.19 Self-Replicating Robots for Space Solar Power (2000) 63
3.20 Three-Dimensional Solid Printing (2000-present) 64
3.21 Bererton Self-Repairing Robots (2000-2004) 67
3.22 Brooks Living Machines Program (2001-present) 68
3.23 Chirikjian Group Self-Replicating Robots (2001-2003) 69
    3.23.1 Prototype 1 (2001) 69
    3.23.2 Remote-Controlled Self-Replicating Robots (2002) 69
    3.23.3 Semi-Autonomous Self-Replicating Robot (2002) 75
    3.23.4 Suthakorn-Cushing-Chirikjian Autonomous Replicator (2002-2003) 75
3.24 Chirikjian Self-Replicating Lunar Factory Concept (2002) 76
3.25 NIAC Phase I Studies on Self-Replicating Systems (2002-2004) 78
    3.25.1 Lipson Self-Extending Machines (2002) 78
    3.25.2 Chirikjian Self-Replicating Lunar Factories (2003-2004) 78
    3.25.3 Todd Robotic Lunar Ecopoiesis (2003-2004) 79
    3.25.4 Toth-Fejel Kinematic Cellular Automata (2003-2004) 79
3.26 Robosphere Self-Sustaining Robotic Ecologies (2002-2004) 81
3.27 Lozneanu-Sanduloviciu Plasma Cell Replicators (2003) 81
3.28 Griffith Mechanical Self-Replicating Strings (2003-2004) 82
3.29 Self-Replicating Robotic Lunar Factory (SRRLF) (2003-2004) 85

Chapter 4. Microscale and Molecular Kinematic Machine Replicators 89
4.1 Molecular Self-Assembly and Autocatalysis for Self-Replication 90
  4.1.1 Self-Assembling Peptides, Porphyrins, Nucleotides and DNA 91
  4.1.2 Self-Assembling Crystalline Solids 93
  4.1.3 Self-Assembling Dendrimers 93
  4.1.4 Self-Assembling Rotaxanes and Catenanes 93
  4.1.5 Self-Assembly of Mechanical Parts and Conformational Switches 94
  4.1.6 Autocatalysis and Autocatalytic Networks 95
4.2 Ribosomes: Molecular Positional Assembly for Self-Replication 96
4.3 Natural Biological Replicators 101
  4.3.1 Prions 101
  4.3.2 Viroids 101
  4.3.3 Viruses 102
  4.3.4 Prokaryotic Cells 103
  4.3.5 Plasmids 104
  4.3.6 Eukaryotic Cells 105
  4.3.7 Mitochondria 107
  4.3.8 Large Metazoans 107
4.4 Artificial Biological Replicators (1965-present) 108
4.5 Biomolecular-Directed Positional Parts Assembly (1994-present) 110
  4.5.1 Positional Assembly Using DNA 110
  4.5.2 Positional Assembly Using Proteins 112
  4.5.3 Positional Assembly Using Microbes and Viruses 114
  4.5.4 Positional Assembly Using Other Biological Means 115
4.6 Feynman Hierarchical Machine Shop (1959) and Microassembly 115
4.7 Shoulders Electronic Micromachining Replicator (1960-1965) 117
4.8 Laing Molecular Tapeworms (1974-1978) 118
4.9 Drexler Molecular Assemblers (1981-1992) 119
  4.9.1 Drexler Generic Assembler (1986) 120
  4.9.2 Drexler Extruding Tube Assembler (1991) 120
  4.9.3 Drexler Nanofactory Replication System (1991-1992) 121
  4.9.4 Feynman Grand Prize (Foresight Institute) 125
4.10 Merkle Molecular Assemblers (1991-2000) 125
  4.10.1 Merkle Generic Assembler (1992-1994) 125
  4.10.2 Merkle Cased Hydrocarbon Assembler (1998-2000) 126
4.11 Extruding Brick Assemblers (1992-2003) 127
  4.11.1 Drexler Minimal Assembler (1992) 127
  4.11.2 Merkle Replicating Brick Assembler (1995-1997) 129
  4.11.3 Merkle-Freitas Hydrocarbon Molecular Assembler (2000-2003) 130
    4.11.3.1 Summary Description 132
    4.11.3.2 Product Object Extrusion 132
    4.11.3.3 The Broadcast Architecture for Control 132
    4.11.3.4 Hydrocarbon Assembler Subsystems 133
4.12 Bishop Overtool Universal Assembler (1995-1996) 135
4.13 Goddard Proposed Assembler Simulation Study (1996) 135
4.14 Zyvex Nanomanipulator Array Assembler System (1997-1999) 135
4.15 Bishop Rotary Assembler (1998) 136
4.16 Hall Factory Replication System (1999) 136
4.17 Zyvex Exponential Assembly (2000) 138
4.18 Freitas Biphase Assembler (2000) 140
4.19 Phoenix Primitive Nanofactory (2003) 141
4.20 Zyvex Microscale Assemblers (2003) 144

Chapter 5. Issues in Kinematic Machine Replication Engineering 145
5.1 General Taxonomy of Replicators 145
  5.1.1 Dawkins Classification of Replicators (1976) 146
  5.1.2 Miller Critical Subsystems of Living Systems (1978) 146
  5.1.3 Hasslacher-Tilden MAP Survival Space (1994-1995) 147
  5.1.4 Szathmary Classification of Replicators (1995-2000) 148
  5.1.5 Sipper POE Model of Bio-Inspired Hardware Systems (1997) 149
  5.1.6 Taylor Categorization of Reproducers (1999) 150
  5.1.7 Bohringer et al Taxonomy of Microassembly (1999) 150
  5.1.8 Suthakorn-Chirikjian Categorization of Self-Replicating Robots (2002-2003) 151
  5.1.9 Freitas-Merkle Map of the Kinematic Replicator Design Space (2003-2004) 152
5.2 Replication Time vs. Replicator Mass 175
5.3 Minimum and Maximum Size of Kinematic Replicators 176
5.4 Efficient Replicator Scaling Conjecture 178
5.5 Fallacy of the Substrate 178
5.6 Closure Theory and Closure Engineering 180
5.7 Massively Parallel Molecular Manufacturing 182
5.8 Software Simulators for Robots and Automated Manufacturing 184
5.9 Brief Mathematical Primer on Self-Replicating Systems 185
  5.9.1 Fibonacci's Rabbits 185
  5.9.2 Strategies for Exponential Kinematic Self-Replication 186
  5.9.3 Limits to Exponential Kinematic Self-Replication 188
  5.9.4 Performance of Convergent Assembly Nanofactory Systems 191
  5.9.5 Power Law Scaling in Convergent Assembly Nanofactory Systems 193
  5.9.6 Design Tradeoffs in Nanofactory Assembly Process Specialization 194
5.10 Replicators and Artificial Intelligence (AI) 195
5.11 Replicators and Public Safety 196

Chapter 6. Motivations for Molecular-Scale Machine Replicator Design 201
6.1 Initial Motivations for Study 201
6.2 Arguments Favoring a Focused Design Effort 201
  6.2.1 Design Precedes Construction 202
  6.2.2 Demonstration of Feasibility 202
  6.2.3 Clarifying the Proposal 204
6.3 Arguments Against a Focused Design Effort 204
  6.3.1 Molecular Assemblers Are Too Dangerous 204
  6.3.2 Molecular Assemblers Are "Impossible" 206
  6.3.3 Assemblers Have Not Yet Been Demonstrated 208
  6.3.4 An Early Design Will Not Speed Development 208
  6.3.5 Assemblers Would Be No Better Than Conventional Alternatives 210
  6.3.6 Potential Design Errors Make the Analysis Inherently Worthless 210
  6.3.7 Macroscale-Inspired Machinery Will Not Work at the Nanoscale 211
  6.3.8 The Design Is Too Obvious 212
6.4 Specific Goals of a Focused Design Effort 212
  6.4.1 Show Feasibility of Molecular Assembler or Nanofactory 212
  6.4.2 Exemplify a Simple Design 213
  6.4.3 Exemplify a Capable Design 214
  6.4.4 Exemplify a Benign Design 215
  6.4.5 Embody Principles of Good Design 215
  6.4.6 Systems and Proposals for Future Research 216
6.5 Focusing on Molecular Assemblers 216

Appendix A — Data for Replication Time and Replicator Mass 219

Appendix B — Design Notes on Some Aspects of the Merkle-Freitas Molecular Assembler 223
B.1 Geometrical Derivation of Assembler Dimensions 223
B.2 Some Limits to Assembler Scalability 224
B.3 Gas Phase vs. Solvent Phase Manufacturing 225
B.4 Acoustic Transducer for Power and Control 225
  B.4.1 Selection of Acoustic Frequency 225
  B.4.2 Physical Description of Acoustic Transducer and Pressure Bands 226
  B.4.3 Piston Fluid Flow Dynamics 227
    B.4.3.1 Bulk Fluid and Laminar Flows 227
    B.4.3.2 Confined-Fluid Density Layering Due to Near-Wall Solvation Forces 228
    B.4.3.3 Piston Operation in the Desorption and Viscous Regimes 229
      B.4.3.3.1 Nature of the Physisorbed Monolayer 229
      B.4.3.3.2 Operational Regimes Defined 229
      B.4.3.3.3 Operation in the Desorption Regime 229
      B.4.3.3.4 Operation in the Viscous Regime 231
      B.4.3.3.5 Physisorption and Desorption of Nonsolvent Molecules 231
  B.4.4 Thermal Expansion, Acoustic Cavitation and Resonance 232
    B.4.4.1 Thermal Expansion in Diamond Walls 232
    B.4.4.2 Transient Cavitation 232
    B.4.4.3 Stable Cavitation 232
    B.4.4.4 Acoustic Heating 232
    B.4.4.5 Acoustic Torque and Fluid Streaming 232
    B.4.4.6 Shock Wave Formation 232
  B.4.5 Energy Efficiency and Energy Cost of Molecular Manufacturing 233
B.5 Wall Stiffness During External Acoustic Forcing, Thermal Noise, or Collision 233
B.6 Wall Stiffness During Internal Mechanical Activities 233
B.7 Wall Sublimation and Mechanical Depassivation Contamination 234

References 235
Index 313

FIGURES

Preface

Figure P.1. Lineage of works in the field of nonbiological kinematic self-replicating machines. xviii

Chapter 1. The Concept of Self-Replicating Machines

Figure 1.1. Vaucanson's duck. 1

Figure 1.2. Dilbert discovers the concept of "replication by proxy." 2

Figure 1.3. Robots made of classical components can make identical copies of themselves and thus self-replicate, but quantum systems cannot. 4

Chapter 2. Classical Theory of Machine Replication

Figure 2.1. Schematic of von Neumann kinematic replicator. 7

Figure 2.2. Finite state automaton cellular space. 8

Figure 2.3. Twenty-nine states of von Neumann's cellular automata. 9

Figure 2.4. Universal construction in the cellular automata model of machine replication, from von Neumann. 9

Figure 2.5. Universal construction arm builds the memory tape in the cellular automata model of machine replication. 10

Figure 2.6. Self-replication of Langton's SR loop. 12

Figure 2.7. BioWall implementation showing genotypic data path and phenotypic representation of Swiss flag. 13

Figure 2.8. Typical run of JohnnyVon program with a seed strand of 8 codons and a soup of 80 free codons. 14

Figure 2.9. Laing's self-reproduction by self-inspection. 17

Chapter 3. Macroscale Kinematic Machine Replicators

Figure 3.1. Artist's conception of Moore's artificial living plant. 19

Figure 3.2. Harvesting Moore's artificial living plants. 20

Figure 3.3. A 1-D self-replicating machine made of parts of two kinds. 21

Figure 3.4. A double-hook "food" unit for Penrose block replicator. 21

Figure 3.5. Activating cam levers for Penrose block replicator. 22

Figure 3.6. Four-unit blocking device for Penrose block replicator. 22

Figure 3.7. Interdigitating bases for Penrose block replicator. 22

Figure 3.8. One replication cycle of the Penrose block replicator. 22

Figure 3.9. Physical replication using Jacobson locomotive toy train cars with fixed plan. 23

Figure 3.10. Physical replication using Jacobson locomotive toy train cars with replicated plan. 24

Figure 3.11. Design of the Morowitz floating electromechanical replicator. 24

Figure 3.12. Replication cycle of the floating electromechanical replicator. 24

Figure 3.13. "Unmanned" robot factory of Fujitsu Fanuc Ltd., reborn in April 1998. 26

Figure 3.14. Fanuc Factory Group: Robot Factory. 27

Figure 3.15. Production mini-plants and assembly plant for production mini-plants. 28

Figure 3.16. Hall's "utility fog" foglets. 29

Figure 3.17. Michael's Fractal Robots. 31

Figure 3.18. Bishop's XY Active Cell and Cell Aggregate. 30

Figure 3.19. "Replicating swarm" of Globus et al. 31

Figure 3.20. Bishop's proposed "Overtool" would assemble individual KCA cells from more primitive part. 31

Figure 3.21. Yim's (A) PolyPod multirobot automaton and (B) PolyBot multirobot automaton in snake mode. 31

Figure 3.22. Yim's PolyBot multirobot automaton reconfigures itself from loop to snake to spider mode. 32

Figure 3.23. A Telecube G2 module fully contracted. 32

Figure 3.24. Telecube configurations and lattice movement. 32

Figure 3.25. CONRO multirobot system (20 modules making two hexapods). 33

Figure 3.26. Distributed self-reconfiguration of 3-D homogeneous modular structure. 33

Figure 3.27. Modular self-reconfigurable robot M-TRAN (Modular TRANSformer) changes its shape from a crawler to a four-legged walking robot. 33

Figure 3.28. I-Cubes: A modular self-reconfiguring robotic system. 34

Figure 3.29. Computer-controlled LEGO® car factory made entirely from LEGO® components. 34

Figure 3.30. A moment in the life of the Robot Jurassic Park. 35

Figure 3.31. Automated space manufacturing facility for the processing of nonterrestrial materials. 36

Figure 3.32. Schematic of a laboratory mass spectrometer, the theoretical basis for Taylor's proposed Santa Claus Machine. 37

Figure 3.33. Project Daedalus interstellar flyby probe, modified to carry a self-replicating seed payload. 39

Figure 3.34. A modern machine shop, in the hands of competent human operators, can replicate most of its own components. 40

Figure 3.36. 1980 NASA Summer Study theme art. 43

Figure 3.35. Comparison of "linear" and "exponentiating" (self-replicating) manufacturing systems. 43
Figure 3.37. Schematic of simple robot self-replication. 45
Figure 3.38. Proposed Robot Replication Feasibility Demonstration. 45
Figure 3.39. Flexible scheduling of self-replicating lunar factory operational phases. 46
Figure 3.40. Functional schematic of unit replication factory. 46
Figure 3.41. Unit replication factory stationary "universal constructor." 47
Figure 3.42. Unit replication factory mobile "universal constructor." 47
Figure 3.43. Unit replication lunar factory. 48
Figure 3.44. Possible growth plan with simultaneous replica construction of a field of lunar factories. 48
Figure 3.45. Functional schematic of unit growth factory. 49
Figure 3.46. Unit growth factory chemical processing sector. 50
Figure 3.47. Unit growth factory parts fabrication sector. 50
Figure 3.48. Unit growth factory assembly sector. 51
Figure 3.49. Unit growth lunar factory. 51
Figure 3.50. Schematic of Freitas atomic separator replicator. 52
Figure 3.51. Atomic separator with power and radiator systems deployed in lunar orbit. 52
Figure 3.52. A field of constructed solar cells with auxons laying track in foreground. 53
Figure 3.53. Carbothermic element separation cycle for Lackner-Wendt auxons. 53
Figure 3.54. Plan view of a system comprising a self-reproducing fundamental fabricating machine. 54
Figure 3.55. Lohn monotype electromechanical replicator: a single-type component and two-component seed unit. 59
Figure 3.56. Lohn monotype electromechanical replicator: self-assembly steps. 59
Figure 3.57. Lohn polytype electromechanical replicator: two component types comprise a single seed unit. 60
Figure 3.58. Lohn polytype electromechanical replicator: self-assembly steps. 60
Figure 3.59. Moses' "basic component" for self-replicating construction machine. 61
Figure 3.60. Moses' component assemblies for self-replicating construction machine. 61
Figure 3.61. Functionality matrix for the component set used in the Moses self-replicating construction machine. 62
Figure 3.62. Moses' self-replicating construction machine. 62
Figure 3.63. Actual physical implementation of Moses' self-replicating construction machine. 63
Figure 3.64. 3D Systems' ThermoJet 3-D printer allows CAD designers to quickly print a 3-dimensional model to 50-100 micron resolution. 64
Figure 3.65. GOLEM Project uses robotic system to automatically design and manufacture new robots. 65
Figure 3.66. An inkjet printed thermal actuator. 65
Figure 3.67. The 3-D gadget printer. 66
Figure 3.68. A 3-D resin-sculpted bull the size of a red blood cell. 67
Figure 3.69. Self-sustaining system of mobile robots. 68
Figure 3.70. Robots capable of mutual repair. 68
Figure 3.71. LEGO®-based teleoperated kinematic replicator: Prototype 1. 70
Figure 3.72. LEGO®-based teleoperated kinematic replicator: Robot 1. 71
Figure 3.73. LEGO®-based teleoperated kinematic replicator: Robot 2. 72
Figure 3.74. LEGO®-based teleoperated kinematic replicator: Robot 3. 73
Figure 3.75. LEGO®-based teleoperated kinematic replicator: Robot 4. 74
Figure 3.76. LEGO®-based fully-autonomous kinematic replicator. 77
Figure 3.77. Architecture for self-replication. 76
Figure 3.78. Depiction of the functioning lunar self-replicating factory. 76
Figure 3.79. KCA unit cell with some tabs and sensors. 81
Figure 3.80. Wang-tile implementations of an op-amp and a NAND gate, using KCA cells configured as electronic wire/transistor components. 81
Figure 3.81. Two steps among many, in a lengthy parts assembly operation involving KCA cells on a base plane platform. 80
Figure 3.82. Robosphere 2002 workshop on self-sustaining robotic ecologies. 80
Figure 3.83. Cellular automaton representation of Griffith linear templating replication. 82
Figure 3.84. Logical scheme and replication cycle of Griffith self-replicating wire. 85
Figure 3.85. Effective rule table for Griffith self-replicating wire. 85
Figure 3.86. Tiling scheme for Griffith self-replicating wire. 84
Figure 3.87. Physical implementation of Griffith self-replicating wire. 84
Figure 3.88. Types of mobile robots at the SRRLF. 87
Figure 3.89. Perspective view of possible motions of robots and gantries on the SRRLF factory floor. 87
Figure 3.90. Functional flowchart of the SRRLF factory in operation. 87
Figure 3.91. SRRLF replication pattern across the lunar surface. 86

Chapter 4. Microscale and Molecular Kinematic Machine Replicators

Figure 4.1. Clarification of one important aspect of the replicator design space. 89
Figure 4.2. Top view of a self-assembled G^C rosette nanotube conjugated to benzo-18-crown-6. 93
Figure 4.3. Structure of 1.7-kilobase single-stranded nanoscale self-folding DNA octahedron. 92
Figure 4.4. Self-assembly of parts using sequential random bin-picking. 94

Figure 4.5. Griffith's mechanical allosteric enzyme. 95
Figure 4.6. Rebek's self-complementary autocatalytic self-replicating molecules. 97
Figure 4.7. The ribosome acts as a programmable nanoscale assembler of protein nanoproducts. 96
Figure 4.8. General 3-D topography of the bacterial ribosome: side and bottom views of the small 30S subunit, the large 50S subunit, and the complete 70S ribosome unit. 96
Figure 4.9. Nucleotide base layout and 3-D folded structure of the 23S rRNA and the 5S rRNA, comprising the large 50S subunit. 99
Figure 4.10. Nucleotide base layout and 3-D folded structure of the 16S rRNA, comprising the small 30S subunit. 98
Figure 4.11. Cycle of positional assembly for the ribosome. 101
Figure 4.12. Schematic image of mouse prion domain PrP(121-321). 100
Figure 4.13. Viroid structure. 103
Figure 4.14. Schematic of the symmetric pathway of viroid replication. 103
Figure 4.15. T4 bacteriophage virus. 102
Figure 4.16. Self-assembly of bacteriophage T4 in ordered sequence from its individual component parts. 102
Figure 4.17. Virus replication strategies. 105
Figure 4.18. Rod-shaped *E. coli* bacteria undergoing cell division. 105
Figure 4.19. Schematic of plasmid replication. 104
Figure 4.20. The eukaryotic cell cycle. 104
Figure 4.21. Schematic representation of the phases of eukaryotic mitosis. 107
Figure 4.22. Schematic of mitochondrial replication. 107
Figure 4.23. A mechanical DNA-based actuator. 110
Figure 4.24. One half-cycle of Yurke's DNA-based actuator. 113
Figure 4.25. Using reversible complementary linkers to actuate linear DNA-based strut in discrete steps. 113
Figure 4.26. Theoretical proposal to combine biomolecular motor molecules and artificial DNA structures with carbon nanotubes. 113
Figure 4.27. Self-assembled protein/nucleic acid molecular camshaft, in 3-lobe and 2-lobe versions. 112
Figure 4.28. Laing molecular tapeworms. 119
Figure 4.29. Cross-section of a stiff molecular manipulator arm, with identification of parts; image of Fine Motion Controller; image of ribosome. 121
Figure 4.30. Drexler extruding tube assembler. 120
Figure 4.31. Drexler factory replicator. 120
Figure 4.32. Drexler's exemplar architecture for convergent assembly. 123
Figure 4.33. Merkle's exemplar architecture for convergent assembly used in Drexler's desktop molecular manufacturing appliance. 122
Figure 4.34. A molecular sorting rotor for the selective importation of molecular feedstock. 125
Figure 4.35. Schematic diagrams of mill-style reactive encounter mechanisms. 125
Figure 4.36. Schematic diagram of a staged cascade molecular sortation process, based on molecular sorting rotors. 124
Figure 4.37. Schematic drawing of the Merkle cased hydrocarbon assembler. 127
Figure 4.38. Schematic illustration of the extruding brick geometry for a molecular assembler. 126
Figure 4.39. A ratchet mechanism driven by a pair of pressure-threshold actuators. 129
Figure 4.40. A positioning mechanism based on the Stewart platform. 128
Figure 4.41. Merkle replicating brick assembler. 128
Figure 4.42. Physical device specifications for the Merkle-Freitas hydrocarbon molecular assembler. 131
Figure 4.43. Replication cycle of Merkle-Freitas assembler. 132
Figure 4.44. Schematic of the broadcast architecture for control. 132
Figure 4.45. Schematic view of Merkle-Freitas assembler subsystems. 132
Figure 4.46. Rotary Assembler. 136
Figure 4.47. A motile parts-assembly robot in Hall factory replicator. 136
Figure 4.48. Rectangular 3-dimensional framework for parts assembly in Hall factory replicator. 136
Figure 4.49. Parts fabricator in Hall factory replicator. 136
Figure 4.50. A detailed view of the wrist assembly of the parts fabricator in the Hall factory replicator. 139
Figure 4.51. System diagram for the bootstrap path of a self-replicating manufacturing system. 139
Figure 4.52. Basic two-component Rotapod™ assembly station. 138
Figure 4.53. Sequence of Rotapod™ assembly operations necessary for the first station to assemble the second. 138
Figure 4.54. Result of five generations of Rotapod™ exponential assembly operations. 141
Figure 4.55. Crude schematic of the fabrication device and assembly device in the Freitas biphase assembler system. 140
Figure 4.56. Nanofactory workstation grid. 143
Figure 4.57. The reliable basic production module. 142
Figure 4.58. Convergent assembly fractal gathering stages. 142
Figure 4.59. Casing and final assembly stage of nanofactory layout. 144

Chapter 5. Issues in Kinematic Machine Replication Engineering

Figure 5.1. The complete MAP survival space. 146
Figure 5.2. The POE taxonomy of bio-inspired systems. 148
Figure 5.4. Block diagram of the Suthakorn-Chirikjian categorization of self-replicating robots. 150
Figure 5.3. Taylor's "Categorization of Reproducers". 151

Figure 5.5. The multidimensional Freitas-Merkle kinematic replicator design space. 153
Figure 5.6. The 1/4-power law for replication time as a function of replicator mass, for biological replicators. 174
Figure 5.7. Generalized closure engineering design cycles. 180
Figure 5.8. Millipede concept of IBM Zurich Research Laboratory 182
Figure 5.9. Successive generations of Fibonacci's rabbits. 184
Figure 5.10. Tree diagram of generation-limited replication for $\eta_{replica} = 2, G = 3$. 189
Figure 5.11. Growth plan overview of a field of self-replicating factories on a planetary surface. 188
Figure 5.12. Limits to exponential and polynomial expansion of self-replicating interstellar probe populations dispersing throughout the galactic disk. 191
Figure 5.13. Cycles in the population dynamics of the snowshoe hare and its predator the Canadian lynx. 191
Figure 5.14. Progression of assembly modules in convergent assembly, with schematic showing positioning of all modules. 190
Figure 5.15. Geometry for a convergent-assembly nanofactory system with a one-fourth power scaling law. 192

Appendix B — Design Notes on Some Aspects of the Merkle-Freitas Molecular Assembler

Figure B.1. Assembler wall dimensions: side view and top view. 225
Figure B.2. Pressure bands for power and control. 226

PREFACE & ACKNOWLEDGEMENTS

The principal goal of molecular nanotechnology (MNT) is to develop a manufacturing technology able to inexpensively manufacture most arrangements of atoms that are consistent with physical law. In terms of its precision, flexibility, and low cost, this will be the ultimate manufacturing technology in human history. Two central mechanisms have been proposed to achieve these goals at the molecular scale: (1) programmable positional assembly and (2) parallel assembly.

Programmable positional assembly at the molecular scale is the central mechanism for achieving both great flexibility in manufacturing and the ultimate in molecular manufacturing precision. (Positional assembly is a manufacturing procedure in which components used in a construction are held in known positions and are constrained to follow desired intermediate physical pathways throughout the entire construction sequence; Chapter 4.) Methods for achieving positional assembly at the molecular scale are currently under active investigation by many research groups worldwide. Some of this work, especially mechanosynthesis work focused on positional assembly of diamond and diamond surfaces, will be the subject of a future publication.[1]

Parallel assembly, whether using self-assembly, large manipulator arrays, or other self-replicating systems, is the central mechanism for achieving low cost manufacturing. (Parallel assembly is a manufacturing procedure in which a large number of product components or product objects are manipulated simultaneously in order to build bigger, more complex, or more numerous product objects; Section 5.7.) Self-replicating machines can make massively parallel manufacturing possible. System architectures by which this goal could be achieved, including specific conceptual architectures for nanofactories or molecular assemblers that should be capable of both molecular manufacturing and mechanical self-replication, are one important objective of the present work.

This book also offers the first general review of the voluminous theoretical and experimental literature pertaining to physical self-replicating systems since the NASA report and survey on self-replicating systems (SRS) which was published in the 1980s (more than 20 years ago).[2] The principal focus here is on self-replicating machine systems. Most importantly, we are primarily concerned with "kinematic"[3,4] self-replicating machines: machine systems in which actual physical objects, not merely patterns of information, undertake their own replication in physical space.

Most of the works described herein are mapped in Figure P.1, showing both the chronological development and the conceptual lineage. Following a brief burst of activity in the early 1980s, the field of kinematic self-replicating machine design received new interest in the 1990s with advances in robotics and an emerging recognition of the feasibility of molecular nanotechnology.[208] The field of kinematic self-replicating robots is currently experiencing an amazing renaissance of research activity among robotics engineers and scientists who have recently recognized that replicating systems are simple enough to permit experimental laboratory demonstrations of working devices on relatively modest research budgets. Despite its comprehensive nature our survey is unavoidably incomplete. For instance, the authors are aware of an impending German patent on a very clever replicator design that will not become public until at least year-end 2004, but which they cannot reveal in these pages due to their nondisclosure agreement with the scientists involved. Other preliminary work has also come to our attention.[5]

This book serves a much-needed purpose in collecting together a wide range of discussions and proposals for machines that can build copies of themselves. Our main focus is twofold: First, to provide a critical review of the literature to give interested researchers a solid foundation from which to initiate their studies, and second, to help focus abstract philosophical discussions of self-replication in more concrete terms, in light of our emerging ability to make such machines. The material is thus of interest to both types of readers — those who are most interested in the general issues, and those who are more technically inclined and eager to begin work on designing and building self-replicating machines. Laing[6] notes that "this access to the original publications of work on machine replicators is invaluable because it makes evident in detail what has already been done, and what therefore need not be repeated, as well as having the additional salutary effect of constraining those who in ignorance make claims of originality for results which may have appeared in the open literature decades earlier."

Raj Reddy, head of the Carnegie Mellon University (CMU) Robotics Institute and co-chair of the President's Information Technology Advisory Committee (PITAC) from 1999-2001, believes that robust self-replicating systems represent one of the "longstanding challenges in the AI area that will be within technological reach in the next twenty years."[7] There is increasing interest from the artificial intelligence and artificial life communities in this research, with M.A. Bedau, T.S. Ray, H. Sayama, and others[8-10] regarding the creation of "an artificial system that demonstrates robust self-replication and evolution in the real physical world [as] among the grand challenges in artificial life." In a July 2003 interview,[11] Steve Jurvetson, a managing director at the California venture capital firm Draper Fisher Jurvetson, noted that "putting a bold, audacious goal out there could be very galvanizing. Whether conceptualized as a universal assembler, a nanoforge, or a matter compiler, I think the 'moon-shot' goal for 2025 should be the realization of the digital control of matter, and all of the ancillary industries, capabilities, and learning that would engender."

Over the last century, research in artificial self-replication has progressed along two major tracks.

The first track of research is the field of cellular or computational self-replication, which investigates self-replication purely in the context of patterns of information, most notably patterns organized and mediated by cellular automata.[200,380-384] This area has received by far the greatest theoretical and experimental attention, because experiments require only general-purpose computer

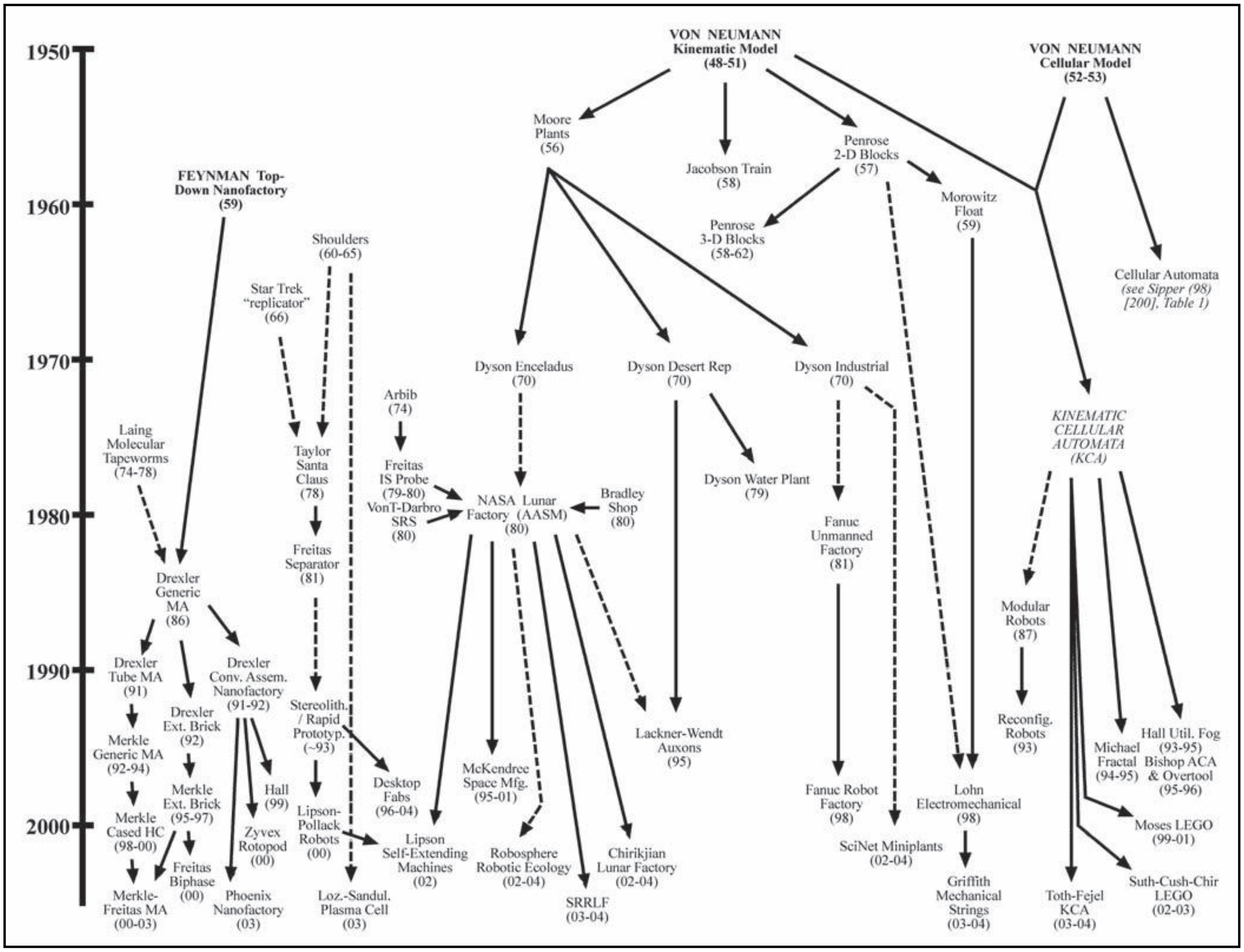

1950
1960
1970
1980
1990
2000
VON NEUMANN Kinematic Model (48-51)
VON NEUMANN Cellular Model (52-53)
Moore Plants (56)
Jacobson Train (58)
Penrose 2-D Blocks (57)
Penrose 3-D Blocks (58-62)
Morowitz Float (59)
FEYNMAN Top-Down Nanofactory (59)
Shoulders (60-65)
Star Trek "replicator" (66)
Cellular Automata (see Sipper (98) [200], Table 1)
Dyson Enceladus (70)
Dyson Desert Rep (70)
Dyson Industrial (70)
Arbib (74)
KINEMATIC CELLULAR AUTOMATA (KCA)
Laing Molecular Tapeworms (74-78)
Taylor Santa Claus (78)
Freitas IS Probe (79-80)
VonT-Darbro SRS (80)
NASA Lunar Factory (AASM) (80)
Bradley Shop (80)
Dyson Water Plant (79)
Fanuc Unmanned Factory (81)
Freitas Separator (81)
Drexler Generic MA (86)
Modular Robots (87)
Drexler Tube MA (91)
Drexler Conv. Assem. Nanofactory (91-92)
Drexler Ext. Brick (92)
Stereolith. / Rapid Prototyp. (~93)
Merkle Generic MA (92-94)
Lackner-Wendt Auxons (95)
Reconfig. Robots (93)
Michael Fractal (94-95)
Hall Util. Fog (93-95) Bishop ACA & Overtool (95-96)
Merkle Ext. Brick (95-97)
Hall (99)
Desktop Fabs (96-04)
McKendree Space Mfg. (95-01)
Fanuc Robot Factory (98)
Lohn Electromechanical (98)
Merkle Cased HC (98-00)
Zyvex Rotopod (00)
Lipson-Pollack Robots (00)
Lipson Self-Extending Machines (02)
Robosphere Robotic Ecology (02-04)
Chirikjian Lunar Factory (02-04)
SciNet Miniplants (02-04)
Moses LEGO (99-01)
Freitas Biphase (00)
Merkle-Freitas MA (00-03)
Phoenix Nanofactory (03)
Loz.-Sandul. Plasma Cell (03)
SRRLF (03-04)
Griffith Mechanical Strings (03-04)
Toth-Fejel KCA (03-04)
Suth-Cush-Chir LEGO (02-03)

Figure P.1. Lineage of works in the field of nonbiological kinematic self-replicating machines.

hardware, along with software for which the grammars, rules and constraints of operation have been more rigorously mathematically defined following the initial investigations of John von Neumann in the early 1950s (Section 2.1.3).

The second track of research is the field of kinematic self-replication, which investigates self-replication in the context of physical machinery that can make copies of itself by employing kinematic operations on physical matter — i.e., movement of materials through physical space in the physical world,[3,4] also pioneered by von Neumann starting in the late 1940s (Section 2.1.2). Here, theoretical and experimental successes have been somewhat fewer and more dearly won — but hardly, as some[12-15] have asserted unsuccessfully,[16,17] nonexistent. Although less research attention has been directed toward the kinematic area than toward the cellular area until fairly recently, this deficit is now being actively and enthusiastically remedied in universities and research laboratories in at least 17 countries (i.e., Canada, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Lithuania, Netherlands, Romania, Russia, Spain, Switzerland, U.K. and U.S.) around the world.

Writing in the final report of an NSF/NASA autonomous manufacturing workshop held in April 2000,[18] George Friedman, Professor of Industrial and Systems Engineering at USC, observed[19,20] that the perception of self-replication research as an intellectual island is an illusion: "There are conjectures that self-replication theory is fundamentally different and separate from the more mainstream robotics research, and that is a reason for its lack of support and disappointing progress. However, ...self-replication has many issues and themes in common with advanced robotic concepts and it would be constructive for future research to consider self-replication — as well as evolution — as a natural intellectual extension of the robotics field. For example, the research agenda at the Space Studies Institute at Princeton considers a continuous spectrum of activities from direct man-in-the-loop, fully teleoperated robotics, increasingly autonomous robotics with AI, fully autonomous robots, cooperating hierarchies of robots, diagnosing and repairing robots, replacement and reconfiguring robots, and finally, self-replicating and evolving robots."

While there are as yet (in 2004) no professional journals exclusively devoted to theory or experiment in self-replication (whether kinematic or cellular), there are many journals in related fields[21] where such research can be published. Readers wishing to keep abreast of the latest developments can visit http://www.MolecularAssembler.com/, the first Internet domain exclusively devoted to molecular assemblers and the online home of this document and related materials.

The authors would welcome, support, and recommend the establishment of a new journal for the field of self-replication engineering. As evidenced by the many and diverse works described in this book, the kinematic replicating systems research community is already of moderate size and growing, if still poorly organized.

Undergraduate and graduate engineering students can find courses or degree programs in macroscale mechatronics (the union of conventional mechanical, electrical, and computer engineering) offered at the following educational institutions: Arizona State University,[22] California Polytechnic State University,[23] California State University at Chico,[24] Carnegie Mellon University,[25] Clemson University,[26] Colorado State University,[27] DLR,[28] Georgia Institute of Technology,[29] Johns Hopkins University,[30] Loughborough University,[31] Massachusetts Institute of Technology,[32] Mechatronical Secondary Vocational School,[33] Michigan State University,[34] Middlesex University,[35] North Carolina State University,[36] Rensselaer Polytechnic Institute,[37] Rice University,[38] San Diego State University,[39] San Jose State University,[40] South Bank University,[41] Stanford University,[42] Swedish Institute of Computer Science,[43] Swiss Federal Institute of Technology Zurich,[44] University of California at Berkeley,[45] University of Dundee,[46] University of Florida,[47] University of Illinois at Urbana-Champaign,[48] University of Linz,[49] University of Melbourne,[50] University of Southern Denmark,[51] University of Twente,[52] University of Utah,[53] University of Western Australia,[54] Vanderbilt University,[55] and the Virginia Polytechnic Institute.[56] Lyshevski[84] has a nice discussion of the current situation in the mechatronics curriculum in engineering education. Institutions offering educational and research opportunities in microelectromechanical systems (MEMS) assembly automation, including micromechatronics,[57,58] and a list of current university and corporate programs in desktop micromanufacturing are listed in Section 4.6.

University programs in nanoscale mechatronics (nanomechatronics), molecular robotics and nanorobotics, nanoelectromechanical systems (NEMS), and nanomanufacturing can be found at: Arizona State University,[59] Brown University,[60] California Institute of Technology,[61] Carnegie Mellon University,[62] Cornell University,[63] Ecole Polytechnique Montreal,[64] IEEE Nanotechnology Council,[65] Nagoya University,[66] New York University,[1448] Northwestern University,[67] Pennsylvania State University,[68] Rensselaer Polytechnic Institute,[69] Rice University,[70] Rutgers University,[71] Swiss Federal Institute of Technology Lausanne,[72] Swiss Federal Institute of Technology Zurich,[73] Technische Universitat Ilmenau,[74] Tohoku University,[75] University of California at Berkeley,[76] University of California at Los Angeles,[77] University of Illinois at Urbana-Champaign,[78] University of Minnesota,[79] University of North Carolina at Chapel Hill,[80] University of Southern California,[81] University of Texas at Austin,[82] and the University of Tokyo.[83]

University and allied programs related to artificial life research can be found at: Brandeis University,[85] Brunel University,[86] California Institute of Technology,[87] Cornell University,[88] Dublin City University,[89] École Polytechnique,[90] George Mason University,[91] German National Research Centre for Information Technology,[92] Hungarian Academy of Sciences and University of Szeged,[93] Iowa State University,[94] Liverpool University,[95] Massachusetts Institute of Technology,[96] Michigan State University,[97] Nagoya University,[98] Napier University,[99] National Research Council (Italy),[100] New England Complex Systems Institute,[101] Reed College,[102] Santa Fe Institute,[103] Soka University,[104] Swiss Federal Institute of Technology,[105] Syracuse University,[106] Trinity College,[107] Universidad de Granada,[108] Universitat Dortmund,[109] Universiteit van Amsterdam (Netherlands),[110] University College London,[111] University of Aarhus,[112] University of Aizu,[113] University of Edinburgh,[114] University of Electro-Communications,[115] University of Guelph,[116] University of Hertfordshire,[117] University of Idaho,[118] University of Illinois at Urbana-Champaign,[119] University of Newcastle upon Tyne,[120] University of New Mexico,[121] University of Pennsylvania,[122] University of Southampton,[123] University of Sussex,[124] University of the West of England at Bristol,[125] and the University of Tokyo.[126]

Specific courses on self-replication are appearing in universities around the world. For example, in Spring 2003 Gregory Chirikjian taught a mechatronics course entitled "Intelligence of Self-Replicating Robots" in the Department of Mechanical Engineering at Johns Hopkins University.[30] In Summer 2003, Hiroki Sayama[127] taught a course entitled "Invitation to Self-Replication Studies" in the Graduate School of Information Science at Nagoya University, Japan, which may continue in future years. Pavel Luksha[128] began teaching a new course "General Theory of Self-Reproduction" at The Higher School of Economics, Moscow, Russia, starting in February 2004.

The present work — *Kinematic Self-Replicating Machines* — would be a suitable text for undergraduate or graduate introductory coursework in kinematic replication theory, kinematic replication engineering, or similar topics.

References [####] are used in this book to denote the source of: (1) a direct quotation (enclosed in quotes), (2) a paraphrased passage (footnoted but not enclosed in quotes), or (3) a specific datum. Citations are also employed to indicate sources of additional information on a given topic, especially collections of literature review papers that would provide a suitable introduction to a given field of study. The authors apologize in advance for any inadvertent instances of unattributed usage of previously published material. Such events should be few but should be brought to the authors' immediate attention for correction in a future edition of this work. An attempt was made to cite primary sources whenever possible, but some references are made to secondary sources believed by the authors to be reliable. References to website URLs which have become unresponsive can often be recovered by consulting the Web Archive at http://www.archive.org/index.html.

Acknowledgements

The authors would like to thank the following 136 people and organizations who provided assistance of various kinds, including reading the manuscript, offering useful comments, providing help in locating information or useful referrals to other researchers or materials, giving reprint permission, or other valuable assistance: Bryant Adams, Scott Adams, Rocky Angelucci, Emanuel F. Barros, Mark A. Bedau, Curt Bererton, David M. Berube, Robert G. Best, Martin Billeter, Forrest Bishop, Karl F. Bohringer, Nick Bostrom, Robert J. Bradbury, David Brin, British Interplanetary Society, William R. Buckley, John Burch, Arthur W. Burks, Alan J. Cann, John Canny, Carlos A. Castro, Gwen V. Childs, Gregory S. Chirikjian, CMU Robotics Institute, Mike Collins, Silvano P. Colombano, Paul Davies, Radu Dogaru, K. Eric Drexler, Freeman J. Dyson, Matthew Ellis, Suren Erkman, Ronald S. Fearing, Hicham Fenniri, Ricardo Flores, Foresight Institute, Stephanie Forrest, George Friedman, Robert A. Frosch, Fujitsu Fanuc Ltd., Timothy S. Gardner, James K. Gimzewski, Saul Griffith, J. Storrs Hall, B. Hasslacher, Tad Hogg, Tim J. Hutton, IBM, Takashi

Ikegami, Institute for Molecular Manufacturing, Neil Jacobstein, JACS, Stepas Janusonis, (Japan) National Institute of Advanced Science and Technology (AIST), Gerald F. Joyce, George Khushf, Gunter von Kiedrowski, Loren W. Knapp, Ron D. Knott, Narayanan M. Komerath, Hans Koops, John R. Koza, Markus Krummenacker, Dennis Kunkel, Ray Kurzweil, Klaus S. Lackner, Richard A. Laing, Chris G. Langton, James B. Lewis, Hod Lipson, Jason Lohn, Pier Luigi Luisi, Pavel O. Luksha, Evan Malone, Daniel Mange, Pierre Marchal, Martin C. Martin, Constantinos Mavroidis, Wil McCarthy, Barry McMullin, Joseph Michael, Marvin Minsky, MIT Media Lab, Hans Moravec, Matt Moses, Arcady R. Mushegian, Nature, Philip van Nedervelde, Chrystopher L. Nehaniv, R.A. Owens, Oxford University Press, Rolf Pfeifer, Christopher J. Phoenix, Valenti Pineda, Jordan Pollack, John N. Randall, Thomas S. Ray, James A. Reggia, Aristides Requicha, Roland Riek, Kazuhiro Saitou, Arthur C. Sanderson, Hiroki Sayama, Science/AAAS, Nadrian C. Seeman, Peter Silcox, Moshe Sipper, Michael Sipser, Cameron Slayden, John Smart, Steven S. Smith, Sigvar Strandh, Scot L. Stride, Hong-Bo Sun, Jackrit Suthakorn, 3D Systems, Tim Taylor, Gianluca Tempesti, Georg von Tiesenhausen, Mark W. Tilden, Marco Tomassino, Tihamer Toth-Fejel, Steve Tung, Peter Turney, University of Massachusetts, Cem Unsal, USC Information Sciences Institute, Ron Weiss, Christopher H. Wendt, Xerox PARC, Mark Yim, Eiichi Yoshida, Eliezer S. Yudkowsky, Bernard Yurke, Demin Zhou, and Zyvex Corporation. We especially thank Zyvex Corporation for providing significant funding to support this research.

The reviewers are to be lauded for undertaking a difficult task and should be held blameless for any errors that remain in the manuscript. The authors are solely responsible for all errors of fact or judgment within these pages. Reports of errata may be transmitted electronically directly to the first author at the following email address: rfreitas@rfreitas.com.

We also thank the publisher and staff at Landes Bioscience, especially Celeste Carlton, for their excellent and professional work on this project, and the artist Diego Linares for the excellent cover art.

Robert A. Freitas Jr., J.D.
Senior Research Fellow
Institute for Molecular Manufacturing

Ralph C. Merkle, Ph.D.
Distinguished Professor of Computer Science
Georgia Institute of Technology

15 April 2004

In 1913, Lee De Forest was prosecuted by U.S. government officials for claiming to potential investors that his company, RCA, would soon be able to transmit the human voice over the Atlantic Ocean. The prosecuting officials argued that his claim was so utterly ridiculous that he was surely ripping off investors. He was ultimately released but not before being admonished by the judge to stop making any more fraudulent claims. The rest, as the old saying goes, "is history."

This...serves as a poignant reminder that the relentless forces of technology can lead to predictions that sound nonsensical or unbelievable to people who do not understand where science and technology is headed. The story holds particular relevance to the broader business community because virtually every industry — including the computer, semiconductor, energy, health care, insurance and manufacturing sectors — will soon be confronted with seemingly nonsensical and unbelievable predictions that are about to be created by the new and emerging science of nanotechnology.

– Jack Uldrich, 2004[129]

Like all revolutionary new ideas, the subject has had to pass through three stages, which may be summed up by these reactions:

1. *"It's crazy — don't waste my time";*
2. *"It's possible, but it's not worth doing";*
3. *"I always said it was a good idea."*

– Arthur C. Clarke, 1968[130]

CHAPTER 1

The Concept of Self-Replicating Machines

For most of human history, man's tools and machines bore no resemblance to living organisms and gave no hint of any commonality between the living and the artificial.[150] In Paleolithic times,[151-158] most machines manufactured by man were primitive bone or wooden sticks, crudely shaped handaxes and flint tools,[157] crudely hewn boats,[156] and the like. It was not until a century of centuries after the Paleolithic era ended, following the development of metallurgy,[159] the birth of agriculture,[160] and the founding of the first civilizations,[161] that humans first manufactured complex artifacts such as ploughs and wheeled vehicles consisting of a large number of interacting parts, and ancient Chinese crossbows[162] and locks.[163] By classical times many artifacts were quite sophisticated, including the famous Alexandrian water clock of Ctesibus,[164] Archimedes' screw,[165,166] Roman military catapults,[165,167] Hero of Alexandria's steam engine[168] and other automatons,[169] and lastly the ancient Antikythera computer[170]—a clocklike mechanism containing 31 intermeshed gears used as a calendrical device to calculate the positions of the sun and the moon.

By the 15th and 16th centuries, Western technology had advanced to the stage where machines began to take on lifelike characteristics.[150] For example, the compound microscope and the telescope, analogous to the vertebrate eye, were invented in 1590 and 1608, respectively. The air pump, providing hydraulic pumping analogous to the heart, was invented in 1654. Machines began to crudely exhibit some of the characteristics and properties of living creatures. The 17th and 18th centuries also saw the first successful attempts at constructing lifelike automata.[171-175] For example, Vaucanson's duck (Figure 1.1), constructed and first exhibited in 1739 by Jacques de Vaucanson (1709-1782), had over one thousand moving parts and was able to appear to eat, drink, defecate, quack, waddle, and flap its wings convincingly.[174-177] Such advances raised the obvious possibility that eventually all the characteristics of life[180-186] might find instantiation in mechanical forms—perhaps even the ability to grow and to reproduce.

Self-replication is a hallmark, though no longer the exclusive province, of living systems. It is a myth, still persistently claimed by some,[150] that "no machine possesses this capacity even to the slightest degree" and that "even the far less ambitious end of component self-assembly has not been achieved to any degree." To the contrary, replication as simple mechanical component self-assembly was first achieved in the 1950s, almost half a century ago (Section 3.3), and LEGO®-based autonomous macroscale replicators have now been built and operated in the laboratory (e.g., Section 3.23). Artificial self-replicating software first appeared in the 1960s, then in later decades rapidly proliferated in the form of worms, viruses, artificial life programs, and diverse other virtual species in code-friendly environments such as personal computers and the internet (Section 2.2.1). The technology presently exists to create artificial self-replicating hardware entities, as evidenced by the numerous theoretical proposals and smattering of good engineering results achieved in the laboratory to date. A comprehensive survey of these proposals and results is a principal subject of this book.

The idea that machines might someday be capable of self-replication is at least hundreds of years old. For example, it is said[1081] that when Descartes (1596-1650) first expressed his idea that the human body was a machine* [187] to his royal student, Queen Christina of Sweden, over 300 years ago, she came up with a cogent question: "How," she asked, "can machines reproduce themselves?"**

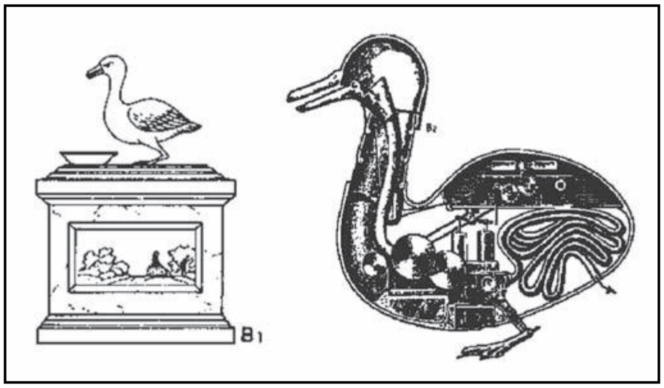


Figure 1.1. Vaucanson's duck. (courtesy of Sigvar Strandh and Dorset Press[177])

---

* *From Descartes'* Treatise on Man:[187] *"I suppose the body to be nothing but a machine . . . We see clocks, artificial fountains, mills, and other such machines which, although only man made, have the power to move on their own accord in many different ways . . . one may compare the nerves of the machine I am describing with the works of these fountains, its muscles and tendons with the various devices and springs which set them in motion . . . the digestion of food, the beating of the heart and arteries . . . respiration, walking . . . follow from the mere arrangement of the machine's organs every bit as naturally as the movements of a clock or other automaton follow from the arrangements of its counterweights and wheels."*

** *In one version[189] of this anecdote, the Queen challenges Descartes' proposition that man is nothing more than a machine by saying: "I never saw my clock making babies." A related variant[190] reports that the Queen pointed to a clock and ordered: "See to it that it reproduces offspring."*

Samuel Butler (1835-1902) gamely attempted to answer her inquiry in his novel *Erewhon*,[188] first published in 1872, when he argued:

> *Surely if a machine is able to reproduce another machine systematically, we may say that it has a reproductive system. What is a reproductive system, if it be not a system for reproduction? And how few of the machines are there which have not been produced systematically by other machines? But it is man that makes them do so. Yes; but is it not insects that make many of the plants reproductive, and would not whole families of plants die out if their fertilization was not effected by a class of agents utterly foreign to themselves? Does anyone say that the red clover has no reproductive system because the humble bee (and the humble bee only) must aid and abet it before it can reproduce? No one. The humble bee is a part of the reproductive system of the clover.**

In a more modern context (Figure 1.2), astronomer Robert Jastrow[192] notes that:

> *The computer—a new form of life dedicated to pure thought—will be taken care of by its human partners, who will minister to its bodily needs with electricity and spare parts. Man will also provide for computer reproduction. Computers do not have DNA molecules; they are not biological organisms. We are the reproductive organs of the computer. We create new generations of computers, one after another....*

About two centuries ago, William Paley[194] (once the Archdeacon of Carlisle) was apparently the first to formulate a teleological argument depicting machines producing other machines.[195] At one point in his 1802 philosophical discourse, after describing a man who finds a stone and a watch, Paley[194] asks his reader to imagine a watch capable of making other watches:

> *Suppose, in the next place, that the person, who found the watch, would, after some time, discover, that, in addition to all the properties which he had hitherto observed in it, it possessed the unexpected property of producing, in the course of its movement, another watch like itself, (the thing is conceivable); that it contained within it a mechanism, a system of parts, a mould for instance, or a complex adjustment of laths, files, and other tools, evidently and separately calculated for this purpose; let us inquire, what effect ought such a discovery to have upon his former conclusion?...The question is not simply, How came the first watch into existence? which question it may be pretended, is done away by supposing the series of watches thus produced from one another to have been infinite, and consequently to have had no such first, for which it was necessary to provide a cause...*

The serious scientific study of artificial self-replicating structures or machines has now been underway for more than 70 years, after first being anticipated by J.D. Bernal[196] in 1929** and by mathematicians such as Stephen C. Kleene who began developing recursion theory*** in the 1930s. Although originally driven by an abiding interest in biology, much of this work has been motivated by the desire to understand the fundamental information-processing principles and algorithms involved in self-replication, even independent of their physical realization.[200] Over the last two decades,[197-228] it has become apparent that a convenient physical realization of replicating machinery—in particular, the molecular assembler (a manufacturing system capable of molecularly precise fabrication or assembly operations)—could also make feasible the manufacture of macroscopic quantities of engineered molecular machine systems, with far-reaching consequences for human progress.[199] But before we can explore specific designs for molecular assemblers, it is necessary to review and contextualize, in this book, the theoretical and experimental foundations for machine self-replication.

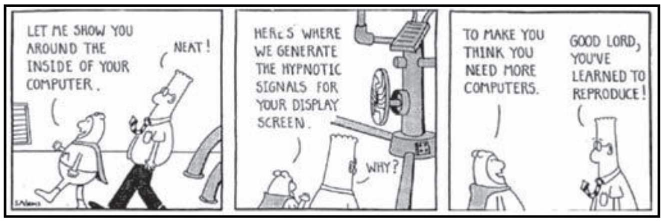

LET ME SHOW YOU AROUND THE INSIDE OF YOUR COMPUTER.
NEAT!
HERE'S WHERE WE GENERATE THE HYPNOTIC SIGNALS FOR YOUR DISPLAY SCREEN.
WHY?
TO MAKE YOU THINK YOU NEED MORE COMPUTERS.
GOOD LORD, YOU'VE LEARNED TO REPRODUCE!

Figure 1.2. Dilbert discovers the concept of "replication by proxy."[193] (© 1994 Scott Adams and Andrews McMeel Publishing, reprinted with permission)

The notion of a machine reproducing itself has great intrinsic interest and invariably elicits a considerable range of responses—some directed toward proving the impossibility of the process, others merely skeptical that it can be carried out, but almost all of them indicating an unwillingness to subject the question to a thorough examination. In discussing self-replication by automata it is essential to establish from the outset some rather important ground rules for the discussion.[242] For example, according to Kemeny:[243] "If [by 'reproduction'] we mean the creation of an object like the original out of nothing, then no machine can reproduce—but neither can a human being....The characteristic feature of the reproduction of life is that the living organism can create a new organism like itself out of inert matter surrounding it."

Often it is asserted that only biological organisms can reproduce themselves. Thus, by definition, machines cannot carry out the process. A related argument, reaching back at least to Leibniz (1646-1716)[244] with echoes even today,[245,246] is the impossibility of fabricating artificial automata which are the equal of divinely created life, cf. Frankenstein[247] and the Golem.**** [248,249] But modern writers[199,1269] would argue that all living organisms are machines and thus the proof of machine reproduction is the biosphere of Earth. This line of reasoning had its genesis at least three centuries ago in the writings of Descartes,[187] and later was picked up by the French materialists of the Enlightenment such as Julien Offroy de La Mettrie (1709-1751),[250] Baron d'Holbach (1723-1789),[251] and Pierre Cabanis (1757-1808),[252] and also by Paley (1743-1805),[194] all of whom asserted that humans are machines. It continued in Samuel Butler's 1863 essay "Darwin Among the Machines," in which Butler perceived the inchoate beginnings

---

** The promotional webpage for the BEAM Robot Games (supported by robot enthusiasts and tinkerers) offers a similar sentiment, quoting roboticist Mark W. Tilden as asserting that while "self-reproducing robots…won't be possible to build (if at all) for years to come," machine evolution involving successive generations of robots can occur if we "view a human being as a robot's way of making another robot," a process Tilden calls "robobiologics".[191]*

*** Stanislaw Ulam, a Polish mathematician who befriended John von Neumann in 1937 and later gave von Neumann the initial idea for cellular automaton replicators, recalled "sitting in a coffeehouse in Lwow in 1929, speculating on the possibility of artificial automata reproducing themselves."[237]*

**** In the present modern context, the recursion theorem says that one can re-write any program so that it will print out a copy of itself before it starts running. More formally, for any Turing machine T, there exists a T′ such that T′ prints out a description of T′ on its tape, and then behaves in exactly the same way as T. Recursion theory was first developed by Stephen C. Kleene[238] and other mathematicians,[239-241] starting in the 1930s.*

***** Similarly, the robots of Karel Capek's historical 1920 science fictional play, "R.U.R. (Rossum's Universal Robots)"[657]—wherein the word "robot" first was coined (the term, derived from the Czech word "robotnik" meaning peasant or serf, was actually suggested to Karel by his brother, Josef)—are manufactured in a factory operated by intelligent robots, but the robots individually lack the knowledge of self-reproduction.[254-256] Says one character in the story, of the robots: "All these new-fangled things are an offense to the Lord. It's downright wickedness. Wanting to improve the world after He has made it."*

of miniaturization, replication, and telecommunication among machines: "I first asked myself whether life might not, after all, resolve itself into the complexity of arrangement of an inconceivably intricate mechanism," Butler recalled in 1880, retracing the development of his ideas.[253] "If, then, men were not really alive after all, but were only machines of so complicated a make that it was less trouble to us to cut the difficulty and say that that kind of mechanism was 'being alive,' why should not machines ultimately become as complicated as we are, or at any rate complicated enough to be called living, and to be indeed as living as it was in the nature of anything at all to be? If it was only a case of their becoming more complicated, we were certainly doing our best to make them so."

Similarly, it is sometimes claimed that although machines can produce other machines, they can only produce machines less complex than themselves.[3] This "necessary degeneracy" of the machine construction process implies that a machine can never make a machine as good as itself. (An automated assembly line can make an automobile, it is said, but no number of automobiles will ever be able to construct an assembly line.) Similarly, Kant (1724-1804)[257] argued that an organism and a watch differ on the basis of the interactions between the parts of the assemblage: "[in a] natural product...the part must be an organ *producing* the other parts—each, consequently, reciprocally producing the others. No instrument of art can answer to this description." These arguments fail if we accept the view of biology as machines, since a human zygote (a single cell) is capable of constructing a vastly more complex structure than itself—in particular, a human being consisting of trillions of specialized cells in a very specific architecture, controlled (at a high level of abstraction) by a brain that is capable of storing many gigabytes, and possibly many terabytes, of data (Section 5.10).* Degeneracy-based arguments are also readily overcome by recognizing the possibility of inferential reverse engineering (Section 2.3.4).

Another common objection is that for a machine to make a duplicate copy it must employ a description of itself. This description, being a part of the original machine, must itself be described and contained within the original machine, and so on, until it appears that we are forced into an infinite regress. A variant of this is the contention that a machine not possessing such a description of itself would have to use itself for a description, thus must have the means to perceive itself to obtain the description.** But then what about the part of the machine that does the perceiving? It cannot perceive itself, hence could never complete the inspection needed to acquire a complete description. All of these self-referential conundrums have been addressed and resolved by theorists, as we shall see below (e.g., Section 2.3.3). For example, a simple answer to the aforementioned problem of self-perception is that the original machine could possess multiple perceiving organs, so that the perceiving could be shared or alternated. Also, there is the question of how detailed a self-description must be for the process to qualify as self-replication—an atomic-level description, a parts-level description, or an active subunits-level description? Amusingly, Eric Benson[259] asks: "How about a robot that could build an identical robot as itself with its own parts? Imagine that the robot takes off its leg, then takes off its other leg, connecting them together, and, after a long process, the robot that was built from those two legs grabs the last remaining part, perhaps the head, and attaches it to itself. What if the goal of the robot was to fit itself through a wall with a tiny hole, and therefore had to dismantle itself pretty thoroughly before rebuilding itself on the other side?" Note that a self-reproducing lifeform does not contain explicit instructions for assembly of the next generation; rather, the genes contain cellular automaton-like rules for assembly (Section 5.1.9).

Yet another related objection is that for the replicative process to be carried out, the machine must come to "comprehend" itself—at which point it is commonly asserted to be well known that "the part cannot possibly comprehend the whole," an argument often voiced in many different contexts[261] and apparently dating back at least to Epicurus (341-270 BC).*** Such disputations reveal that there has historically been a very deep-seated resistance to the notion of machines reproducing themselves,**** as well as an admittedly strong fascination with the concept. The Hungarian-American mathematician John von Neumann, the first scientist to seriously come to grips with the problem of machine self-replication, once noted that it would be easy to cause the whole problem to go away by making the elementary parts of which the offspring machine was to be composed so complex as to render the problem of replication trivial.[262] For example, participants in a NASA study on machine replication[2] noted that a robot required only to insert a fuse in another similar robot to make a duplicate of itself would find self-replication very simple. Similarly, a falling-domino automaton could readily self-replicate on a substrate consisting of a large array of previously edge-positioned dominoes[263]—sometimes called "trivial self-reproduction"* [354-357]—and fire** may similarly be considered a simple replicating entity.[264] The domino example can be regarded as a mechanical analog to autocatalysis (Section 4.1.6), another very simple form of self-replication. And Stewart[265] has suggested that "a letter [page of text] is a self-replicating machine in an environment of photocopiers."***

---

* *Kantian arguments regarding the differences between living and non-living things have been revived recently with discussions of the nature of life in biology, wherein it is claimed that a human, or a living organism in general, cannot be represented as a machine because of the continuous, or quantum, nature of living systems vs. the discrete, or Newtonian, nature of computers and machinery—the central argument being that life has a fractal nature which can only be digitalized through an infinite number of operations.[258] However, Luksha[128] notes that even if self-replication in living systems could not be digitalized, this would only mean that we cannot properly model this process with the "discrete" tools that we usually try to apply, including cellular automata. A self-reproducing machine would operate in the real world, thus would be subject to all laws of physical reality, and through this could produce the same non-linear behavior.*

** *Writes Hofstadter:[260] "Imagine that you wish to have a space-roving robot build a copy of itself out of raw materials that it encounters in its travels. Here is one way you could do it: make the robot symmetrical, like a human being. Also make the robot able to make a mirror-image copy of any structure that it encounters along its way. Finally, have the robot be programmed to scan the world constantly, the way a hawk scans the ground for rodents. The search image in the robot's case is that of an object identical to its own left half. The robot need not be* aware *that its target is identical to its left half; the search can go on merrily for what seems to it to be merely a very complex and arbitrary structure. When, after scouring the universe for seventeen googolplex years, it finally comes across such a structure, then of course the robot activates its mirror-image-production facility and creates a right half. The last step is to fasten the two halves together, and presto! A copy emerges. Easy as pie—provided you're willing to wait seventeen googolplex years (give or take a few minutes)....What we'd ideally like in a self-replicating robot is the ability to make itself literally from the ground up: let us say, for instance, to mine iron ore, to smelt it, to cast it in molds to make nuts and bolts and sheet metal and so on; and finally, to be able to assemble the small parts into larger and larger subunits until, miraculously, a replica is born out of truly raw materials. This was the spirit of the Von Neumann Challenge...this 'self-replicating robot of the second kind'."*

*** *Working from Furley's translation[266] of Epicurus' "Letter to Herodotus", Kenyon[267] summarizes Epicurus' argument as follows: "The impossibility of completing an infinite sequence of contemplation of parts is grounds for rejecting infinite divisibility....(a) We clearly comprehend a whole finite object. (b) To comprehend a whole object, we must comprehend its parts. (c) If its parts are infinite in number, then we cannot complete a sequential process of comprehending each part. (d) Therefore, we cannot comprehend its parts. (e) Therefore, we cannot comprehend the whole object."*

**** *Upon encountering the fully-automated robot factory on the fictional planet Geonosis, in* Star Wars, Episode II *(2002), the ever-talkative golden humanoid robot C3PO exclaims: "What's this? Machines making machines? How perverse!"*

Reproduction vs. Replication. Sipper[200,2430] makes a clear distinction between two terms, "reproduction" and "replication," which are often considered synonymous and sometimes used interchangeably.[262] According to Sipper, "reproduction" is a phylogenetic (evolutionary) process, involving genetic operators such as crossover and mutation, thereby giving rise to variety and ultimately to evolution.[2431] Reproduction is almost synonymous with Luisi's simplest definition[270] of life: "a self-sustaining chemical system undergoing Darwinian evolution." Evolution and mutation are characteristics of biological systems and are highly undesirable in mechanical molecular assemblers,[271] and so machine "reproduction" will not be extensively considered in this book. By contrast, machine "replication" can be a completely planned, purely deterministic process, involving no randomization or genetic operators, which results in an exact physical, or functional, designed duplicate of a parent entity. Most simply,**** self-replication is the process by which an object or structure makes a copy of itself. Others including Sanchez et al[2432] and Adams and Lipson[272] also see a clear distinction between replication and reproduction: "Replication seeks to copy an entire system without error, while reproduction includes a developmental process that allows for variations."[272] In the context of chemical self-replicating systems, Paul and Joyce[1372] note: "Self-replication alone is not sufficient for life unless it allows for the possibility of heritable mutations." From the standpoint of the safety of a new technology, artificial replicators can be made "inherently safe" (Section 5.11) but most artificial reproducers probably cannot be (Section 5.1.9 (L)).

This distinction apparently began with von Neumann[3] (p. 86): "One of the difficulties in defining what one means by self-reproduction is that certain organizations, such as growing crystals, are self-reproductive by any naive definition of self-reproduction, yet nobody is willing to award them the distinction of being self-reproductive. A way around this difficulty is to say that self-reproduction includes the ability to undergo inheritable mutations as well as the ability to make another organism like the original [i.e., make a copy]." The mere ability to make a viable copy, but not to undergo heritable mutation, is therefore not self-reproduction but only self-replication. Self-replication thus represents a restricted, safer form of the more general concept of self-reproduction—unlike reproducers, replicators may be incapable of acquiring any significant variations, or, if variation is acquired, may become nonfunctional.

Szathmary and Smith[2415] note that "whole genomes, symbiotic organelles, cells within organisms, and sexual organisms within societies are certainly always vehicles, but rarely replicators. Their structure is usually not transmitted through copying....Existing organisms are not replicators: they do not reproduce by copying. Instead, they contain DNA that is copied, and that acts as a set of instructions for the development of the organism. Hence reproduction requires both copying and development." George Dyson[274] agrees: "Biological organisms, even single-celled organisms, do not [merely] replicate themselves; they host the replication of genetic sequences that assist in reproducing an approximate likeness of themselves." For the remainder of this book, we shall focus primarily on entities that are capable of "replication," and not "reproduction," as herein defined. Following Sipper[200,2430] and Dawkins,[275] we define "replicator" most simply as an entity that can give rise to a copy of itself. This copy may be an extremely close copy of itself (Figure 1.3), though apparently not an *exact* copy at the quantum level of fidelity.[276]

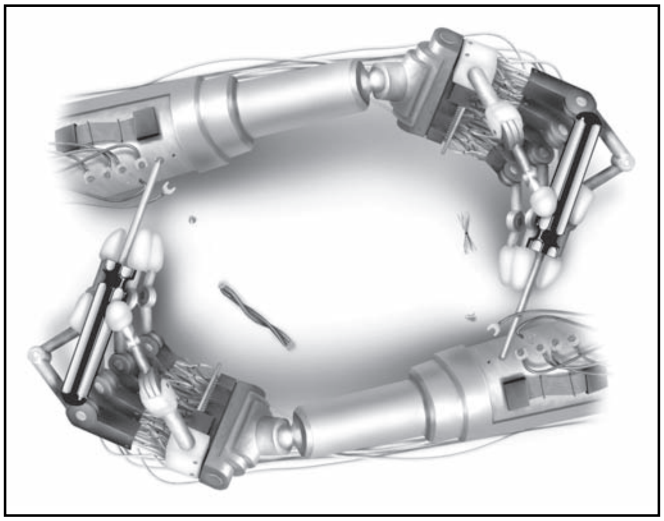


Figure 1.3. Robots made of classical components can make identical copies of themselves and thus self-replicate, but quantum systems cannot.[276] (image courtesy of Cameron Slayden and Science/AAAS[277])

Our discussion of machine replication in this book briefly reviews the foundations of classical machine replication theory (Chapter 2), then describes specific proposals and realizations of macroscale kinematic machine replicators (Chapter 3) and specific proposals, realizations, and naturally-occurring instances of microscale or molecular kinematic machine replicators (Chapter 4). We then close this discussion with a brief summary of selected issues in machine replication theory including minimum replicator size and replication speed, closure engineering, massively parallel manufacturing, the exponential mathematics of replication, and most importantly a comprehensive new overview of the kinematic machine replicator design space which is presented here for the first time (Chapter 5). The book ends with a few thoughts on motivations for undertaking design studies to develop molecular-scale machine replicators, including molecular assemblers and nanofactories (Chapter 6).

** For example, in 1973, Herman[357] argued that "the existence of a self-reproducing universal computer-constructor in itself is not relevant to the problem of biological and machine self-reproduction. There is a need for new mathematical conditions to insure non-trivial self-reproduction."*

*** It has been proposed that the birth of supergiant stars in vast molecular gas clouds may follow a similar "replicative" process, with radiation from early stars triggering compression of adjacent cloud materials, resulting in the first crop of stars replicating a second crop in the adjacent space, and so on, until the cloud is exhausted of its material.[268]*

**** In situations like the paper letter which is regarded as a replicator in a room full of photocopiers, Bryant Adams[269] notes that "a paper with a $50 coupon might be a better replicator than one with uninteresting information as it induces more assistance from the environment, despite not doing much of anything itself."*

***** The effort to define replication in a legally clear fashion during the writing of the Zyvex exponential assembly patent[273] (an effort in which both authors, Merkle and Freitas, participated during early 2000) resulted in an explosion of claims covering numerous mechanisms, alternatives, and exceptions.*

CHAPTER 2

Classical Theory of Machine Replication

The early history of machine replication theory is largely the record of von Neumann's thinking on the matter during the 1940s and 1950s, particularly his kinematic and cellular models, described below. Von Neumann did not finish or publish most of his work on this subject prior to his untimely death in 1957, but Arthur Burks, a colleague of von Neumann, extensively edited and completed many of von Neumann's manuscripts on the subject. Automata theory has advanced and been refined in the decades since, with many alternative models of machine replication having been proposed and discussed as will be described later. By 1980, a detailed technical study co-edited by Freitas[2] concluded that "there appear to be no fundamental inconsistencies or insoluble paradoxes associated with the concept of self-replicating machines." Physics professor Jeremy Bernstein concurred:[1040] "I believe, on the basis of the history of technology, that human nature is such that whatever can be constructed, in theory, will, eventually, be constructed. Since self-replicating automata are possible in principle, they will, I think, eventually be built. When, by whom, and what for, I do not have the foggiest idea."

The following is a brief overview of the classical theory of machine replication from the 1940s to the present. Mathematically inclined readers are encouraged to study the original literature for more rigorous details of various proofs which are beyond the scope of this book.

Some of the material in this Chapter borrows extensively (and appreciatively) from R. Laing's summary of pre-1980 replication theory that originally appeared as a major portion of Section 5.2 of Freitas and Gilbreath,[2] and from two of Burks' edited texts.[3,4]

2.1 Von Neumann's Contributions

John von Neumann[3] "was born on December 28, 1903 in Budapest, Hungary, and died in Washington, D.C., on February 8, 1957. He earned a doctorate in mathematics from the University of Budapest and an undergraduate chemistry degree from the Eidgenossische Technische Hochschule in Zurich, Switzerland. In 1930 he came to the United States as a visiting lecturer at Princeton University, where he was made full professor in 1931. In 1933 he joined the newly formed Institute for Advanced Study as a professor and retained that post for the rest of his life."

Von Neumann[3,300,301] began studying automata replication because he was interested in very complex machines and their behaviors. Von Neumann had a tremendous range of interests — he contributed to the logical foundations of quantum theory, was the co-inventor of the theory of games, and he worked on the Manhattan Project (contributing to the design of the implosion mechanism for the plutonium bomb). It is believed that his participation in the Manhattan Project and the tremendous volume of calculations* necessary for bomb design led him into automatic computing. Hearing of the ENIAC computer project at the Moore School of Electrical Engineering at the University of Pennsylvania, von Neumann was fascinated by the potential of a computer very much faster than any of the devices that had previously been produced.[1011] In the early 1940s there existed only simple relay machines and analog devices such as the differential analyzer. But the new electronic machines that interested von Neumann** promised to be perhaps millions of times faster than relay machines.

Von Neumann immersed himself in the ENIAC project, the first electronic computer program where some actual useful computing was produced. In late 1945 and early 1946, the first problems that were put on ENIAC are believed to have been calculations involving the feasibility of a hydrogen bomb. Von Neumann, although he remained very much interested in nuclear energy and was appointed a member of the Atomic Energy Commission, was more fascinated with the idea of large and complex computing machines.

** Von Neumann had an uncanny ability to solve very complex calculations in his head, a source of wonderment to mathematicians and physicists alike. Goldstine[302] illustrated this quality with an amusing personal anecdote:*

"One time an excellent mathematician stopped into my office to discuss a problem that had been causing him concern. After a rather lengthy and unfruitful discussion, he said he would take home a desk calculator and work out a few special cases that evening. Each case could be resolved by the numerical evaluation of a formula. The next day he arrived at the office looking very tired and haggard. On being asked why, he triumphantly stated he had worked out five special cases of increasing complexity in the course of a night of work; he had finished at 4:30 in the morning.

"Later that morning von Neumann unexpectedly came in on a consulting trip and asked how things were going, whereupon I brought in my colleague to discuss the problem with von Neumann. We considered various possibilities but still had not met with success. Then von Neumann said, 'Let's work out a few special cases.' We agreed, carefully not telling him of the numerical work in the early morning hours. He then put his eyes to the ceiling and in perhaps five minutes worked out in his head four of the previously and laboriously calculated cases! After he had worked about a minute on the fifth and hardest case, my colleague suddenly announced out loud the final answer. Von Neumann was completely perturbed and quickly went back, and at an increased tempo, to his mental calculations. After perhaps another minute he said, 'Yes, that is correct.' Then my colleague fled, and von Neumann spent perhaps another half hour of considerable mental effort trying to understand how anyone could have found a better way to handle the problem. Finally, he was let in on the true situation and recovered his aplomb."

*** According to one writer,[303] von Neumann initially kept his thoughts on machine replication quite private. When Norbert Wiener jokingly wrote to him: "I am very much interested in what you have to say about the reproductive potentialities of the machines of the future...it may be an opportunity for a new Kinsey report," von Neumann denied any contact with the media concerning his theories.[304]*

He devised the organization still employed today in almost all general purpose computational machines — the concept of a serially processed stored program,[1011] or the "von Neumann architecture" or "von Neumann machine." After that work was completed he began thinking seriously about the problems of extremely large machines — their reliability, programming, design, and how to understand what they do — and he became involved with the many possible analogies to the complex behaviors of living systems.[305,306]

2.1.1 A Logical Organization of Self-Replication

Von Neumann set for himself the goal of showing what the logical organization of a self-replicating machine might be. He had in mind a full range of self-replicating machine models which he intended to explore, including the (a) kinematic machine, (b) cellular machine, (c) neuron type machine, (d) continuous machine, and (e) probabilistic machine. Von Neumann ultimately produced only a very informal description of the kinematic machine, and although he wrote a great deal on the cellular machine, his magnum opus on the subject was left in the form of unfinished notes at the time of his death in 1957.[3,4] His other three models were left largely unexplored and will not be discussed further here in great detail.*

Von Neumann[3] concluded that the following characteristics and capabilities were sufficient for machines to replicate without degeneracy of complexity:

- Logical universality — the ability to function as a general-purpose computing machine able to simulate a universal Turing machine (an abstract representation of a computing device, which itself is able to simulate any other Turing machine).[310,311] This was deemed necessary because a replicating machine must be able to read instructions to carry out complex computations.
- Construction capability — to self-replicate, a machine must be capable of manipulating information, energy, and materials of the same sort of which it itself is composed.
- Constructional universality — In parallel to logical universality, constructional universality implies the ability to manufacture any of the finitely sized machines which can be formed from specific kinds of parts, given a finite number of different kinds of parts but an indefinitely large supply of parts of each kind.

Self-replication follows immediately from the above, since the universal constructor** must be constructible from the set of manufacturable parts. If the original machine is made of these parts, and it is a constructible machine, and the universal constructor is given a description of itself, it ought to be able to make more copies of itself.

Von Neumann thus hit upon a deceptively simple architecture for machine replication.[3] The machine would have four parts — (1) a constructor "A" that can build a machine "X" when fed explicit blueprints of that machine; (2) a blueprint copier "B"; (3) a controller "C" that controls the actions of the constructor and the copier, actuating them alternately; and finally (4) a set of blueprints $\phi(A + B + C)$ explicitly describing how to build a constructor, a controller, and a copier. The entire replicator may therefore be described as $(A + B + C) + \phi(A + B + C)$. Now, for the machine "X" that is to be manufactured, let us choose $X = (A + B + C)$. In this special case, Controller C first actuates copier B which copies $\phi(A + B + C)$ to produce a second copy $\phi(A + B + C)$, then actuates constructor A to build a second constructor, copier, and controller — i.e., another $(A + B + C)$ — and to tie them together with the second copy of the blueprints. Thus the automaton $(A + B + C) + \phi(A + B + C)$ produces a second automaton $(A + B + C) + \phi(A + B + C)$ and so self-replication has taken place. The fact that the description $\phi(A + B + C)$ must be both copied (*uninterpreted* data) and translated (*interpreted* data) during replication is the key to avoiding the paradox of self-reference. Note that this replication takes place in an environment of stockroom parts (Section 2.1.2).

Von Neumann[3] also pointed out that if we let $X = (A + B + C + D)$ where D is any arbitrary automaton, then $(A + B + C) + \phi(A + B + C + D)$ produces $(A + B + C + D) + \phi(A + B + C + D)$, and "our constructing automaton is now of such a nature that in its normal operation it produces another object D as well as making a copy of itself." In other words, it can create useful non-self products in addition to replicating itself and has become a productive general-purpose manufacturing system. Alternatively, it has the potential to evolve by incorporating new features into itself.

Observers[314-316] have noted that von Neumann's early schema was later confirmed by subsequent research on the molecular biology of cellular reproduction, with von Neumann's component "A" represented by the ribosomes (Section 4.2) and supporting cellular mechanisms, component "B" represented by DNA polymerase enzymes, component "C" represented by repressor and derepressor

---

* According to Laing:[2] "In addition to his kinematic and cellular models, von Neumann planned to examine three other models of self-reproducing machines. These were to be a neuronal or "excitation-threshold-fatigue" model, a continuous model, and a probabilistic model. Von Neumann is not known to have left any completed work whatsoever on these models at the time of his death, so his intentions are almost entirely a matter of conjecture."

"Following Burks' speculations on this matter,[3] we can guess that von Neumann's **neuronal system** might have been a version of the cell-space model in which the individual cell automata in the space were to be constructed of neuron-like elements. This would have been a rather straightforward process, as it is well known that idealized neurons of the McCulloch-Pitts[307] variety can be employed to implement the kinds of logical gatings and delays called for in the 29-state cell automaton system (Section 2.1.3). The reason for employing neuron-like elements seems mainly an attempt to recast the model in a more "biological" vocabulary."[2] Tempesti[308] adds that a careful analysis of von Neumann's intentions suggests that this model "would have borne a fairly close relationship to today's artificial neural networks, with the addition of some features which would have both increased the resemblance to biological neurons and introduced the possibility of self-replication."

"Von Neumann's postulated **continuous model** might have been an attempt to comprehend machine reproduction in an even more biological format. The usual mathematical tools for handling actual neuron activity are differential equations expressing the electrochemical flows through and along neuron soma and axons. Thus the actions of cell automata (implemented with neurons) could be expressed by sets of differential equations. In this way the more highly developed tools of mathematical analysis might be employed in representing the behavior of the machine system, in contrast to the use of combinatorics which von Neumann himself characterized as one of the most intractable of mathematical specialties."[2]

"Finally, in his proposed **probabilistic model** von Neumann perhaps intended to consider using whole congeries of neuron-like elements in implementing the behaviors of what in the neuronal model could be carried out by single neurons. By employing redundancy techniques similar to those described in his classic paper on reliability,[309] von Neumann may finally have hoped to design a reliable, biologically oriented, self-reproducing machine characterizable by differential equations."[2] Again, Tempesti[308] adds: "We know that von Neumann intended to introduce a kind of automaton where the transitions between states were probabilistic rather than deterministic. Such an approach would allow the introduction of mechanisms such as mutation and thus of the phenomenon of evolution in artificial automata. Once again, we cannot be sure of how von Neumann would have realized such systems, but we can assume they would have exploited some of the same tools used today by genetic algorithms."

** McMullin[312,313] suggests that the issue of "universal construction" is perhaps a bit more subtle and that closure engineering (Section 5.6) may be a challenging endeavor in some applications: "In brief, the definition of a 'universal' set of automata is highly context dependent (in contrast to the definition of a 'universal' set of computations). As a result, it is not trivial to ensure that any proposed, 'universal' constructor is, indeed, a member of the set of machines which it can construct. Von Neumann finessed (and obscured) this point by implicitly restricting attention to 'initially quiescent' automata in his particular cellular automaton formulation. Of course, in general, construction 'universality' is absurdly overkill if one simply wants to achieve self-replication. Much lesser capabilities would suffice for that."

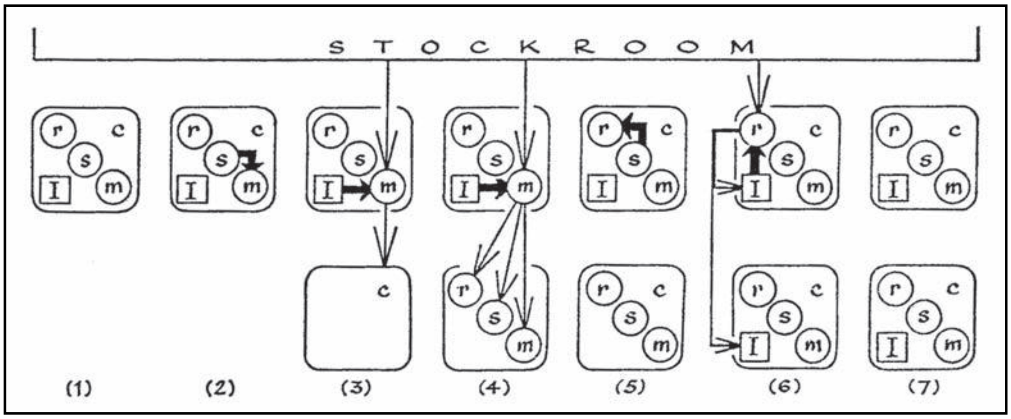


Figure 2.1. Schematic of von Neumann kinematic replicator, from Cairns-Smith.[319]
The kinematic replicator machine consists of a chassis "c" which holds a box of instructions [I], machinery (m) and (r) for acting on and for replicating the instructions, respectively, and a time-switch or sequencer (s). Replication proceeds as follows:[319]

1. Resting phase.
2. Sequencer turns on (m).
3. (m) makes another chassis from materials in the stockroom, following instructions drawn from [I].
4. (m) makes and installs another manufacturing unit (m), another instruction replicator (r), and another sequencer (s). (The latter is possible because this machinery is being instructed from outside itself.)
5. Sequencer turns off (m) and turns on (r).
6. (r) takes recording material (e.g., blank punch cards or magnetic tape) from the stockroom and duplicates [I], then installs the copied instructions in the offspring machine, producing a second machine identical to the first.
7. Resting phase....

molecules and associated expression-control machinery in the cell, and finally component "ϕ(A + B + C)" represented by the genetic material DNA that carries the organism's genome. (The correspondence is not complete: cells include additional complexities.) More importantly, the dual use of information — both interpreted and uninterpreted, as in von Neumann's machine schema — was also found to be true for the information contained in DNA.

2.1.2 The Kinematic Model of Machine Replication

The kinematic model is the one people hear about most often in connection with von Neumann's work on self-replicating machines, probably because it received the earliest attention and publicity.[3,4] Following his first lectures in 1948[317] and 1949,[318] von Neumann's original lecture detailing this model was published[317] in 1951, and in 1955 a further description[243] appeared in the magazine *Scientific American*, authored by John Kemeny.

The notion of kinematic machine replication was dealt with only informally by von Neumann. The mathematician envisioned a physical machine residing in a "sea" or stockroom of spare parts (Figures 2.1 and 3.38). The machine has a memory tape which instructs it to go through certain mechanical procedures. Using a manipulative appendage and the ability to move around in its environment, the device can gather and connect parts. The tape-program first instructs the machine to reach out and pick up a part, then to go through an identification routine to determine whether the part selected is or is not the specific one called for by the instruction tape. If not, the component is thrown back into the "sea" and another is withdrawn for similar testing, and so on, until the correct one is found. Having finally identified a required part, the device searches in like manner for the next, then joins the two together in accordance with instructions. The machine continues following the instructions to make something, without really understanding what it is doing. When it finishes, it has produced a physical duplicate of itself. Still, the second machine does not yet have any instructions, so the parent machine copies its own memory tape onto the blank tape of its offspring.[278] The last instruction on the parent machine's tape is to activate the tape of its progeny.

As Drexler[208] pithily observed: "It may seem somehow paradoxical that a machine can contain all the instructions needed to make a copy of itself, including those selfsame complex instructions, but this is easily resolved. In the simplest approach, the machine reads the instructions twice: first as commands to be obeyed, and then as data to be copied. Adding more data does not increase the complexity of the data-copying process, hence the set of instructions can be made as complex as is necessary to specify the rest of the system. By the same token, the instructions transmitted in a replication cycle can specify the construction of an indefinitely large number of other artifacts."

Von Neumann's original kinematic machine was envisioned as consisting of an assembly of electromechanical units resembling transistors on metallic members with electromagnets and sensing pickups.[440,441] As few as eight different types of elementary parts might be required:[3] four logic elements that receive or transmit stimuli, including (1) a stimulus organ (that realizes the truth function "p or q"), (2) a coincidence organ ("p and q'), (3) an inhibitory organ ("p and not-q"), and (4) a stimuli-producing organ (serving as a source of stimuli); and four mechanical elements, including (5) a rigid member (an insulated girder carrying no stimuli that can form a rigid frame), (6) a fusing organ (which welds or solders two parts together when stimulated), (7) a cutting organ (which unsolders a connection when stimulated), and (8) a muscle (normally rigid, connected to other parts, producing motion when stimulated, and remaining contracted as long as it is stimulated). To acquire the proper parts from the "sea," the machine would have to contain a device which catches and identifies any part that floats into contact with the device. Von Neumann suggested two stimulus units protruding from the constructing automaton. When a part touches them, tests can be made to see what kind of part it is. For example, a stimulus organ will transmit a signal; a girder will not. A muscle might be identified by determining that it contracts when stimulated.

The memory tape is described[4] as a binary tape made of a zigzag arrangement of the rigid elements (girders). Each intersection holds a binary digit or bit of information: "1" is represented by a protruding girder attached to the intersection, and "0" by the absence of a protruding girder. The replicator can move itself relative to the memory tape by means of kinematic elements. It can change a "1" to a "0" by separating a protruding girder from the tape intersection to which it is attached. It can change a "0" to a "1", or extend the tape, by sensing a girder floating on the "sea" with a sensor element, picking up the girder, placing it in position using a kinematic element, and connecting it to the tape by means of a fusing element.

This model thus deals with the geometric-kinematic problems of movement, contact, positioning, fusing, and cutting, but still ignores problems of force and energy (especially energy source, absorption, and dissipation). Von Neumann disregarded the fuel and energy problem in his first design attempt, planning to consider it later, perhaps by introducing a battery as an additional elementary component. But the full kinematic machine was never realized in hardware, nor even fully designed, in part because of von Neumann's premature death in 1957. The total number of machine parts (of at least eight different parts types) in a kinematic replicator was thought to be large, possibly running "into the hundreds of thousands, or millions."[440]

Von Neumann's logical organization for a kinematic self-replicating machine is not the only one possible, but probably is one of the simplest ways to achieve completely self-contained machine replication. In its underlying logic it is very close to the way living organisms seem to reproduce themselves.[320,1042] As is the case with living systems (Section 4.3), the constitutive parts are supplied free to the replicating machine, and those parts are of a relatively high order. That is, the machine dwells in a universe which supplies precisely the sorts of things it needs (Section 5.6) as a kinematic device to make a duplicate of itself — much like living cells residing in a bath of dissolved oxygen, glucose, and nutrients.

Our survey of specific kinematic replicator designs and models is in Chapters 3 and 4.

2.1.3 The Cellular Automaton (CA) Model of Machine Replication

Von Neumann evidently was dissatisfied with his original kinematic model because of its seeming mathematical inelegance. The kinematic model, while qualitatively sound, appeared not easily susceptible to mathematically rigorous treatment and so might not serve to convince a determined skeptic. Von Neumann apparently began work on his first manuscript[321] to describe the cellular model in the Fall of 1952, then worked on it until sometime in late 1953, but never completed the full design of his cellular self-reproducing automaton. The work was first presented publicly in the last of four Vanuxem Lectures delivered at Princeton during 2-5 March 1953. This original work was later edited and published in full in 1966 by Burks.[321]

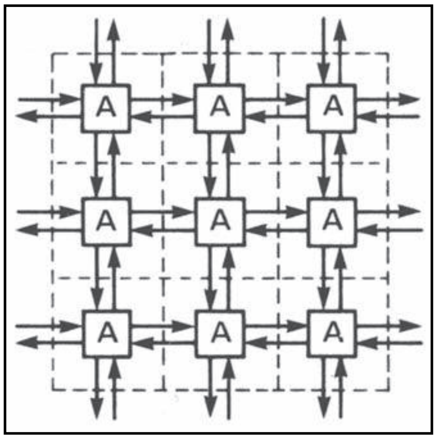


Figure 2.2. Finite state automaton cellular space, from von Neumann.[4]

Sometime in the late 1940s, Stanislaw Ulam,[322] a Polish-American mathematician who had also worked on the Manhattan Project, suggested to von Neumann that the notion of a self-replicating machine would be amenable to rigorous treatment if it could be described in a "cell space" format — a geometrical grid or tessellation, regular in all dimensions.* Within each cell of this system resides a finite state automaton. These cell automata can only be affected by certain of their neighbors, and only in very specific ways. In the model von Neumann finally conceived,** a checkerboard system is employed with an identical finite state automaton in each square (Figure 2.2). In this system, as it evolved with subsequent research, the cell automata can be in one of 29 possible different states (Figure 2.3). Each automaton can communicate with its four cardinal direction (i.e., up, down, left, right) neighbors. The state of a cell automaton (CA) is determined by its own state and by the states of its cardinal direction neighbors.***

At the beginning of operation, all but a finite number of the cell automata are in a "U" or "unexcitable" state. If a given cell is in the "U" state, and all its neighbors also are in the "U" state, then at the next moment of time, the given cell remains in the "U" state. Thus the "U" states can be viewed as representing undifferentiated, passive underlying substrate. Their passivity implies that they may in some cases serve as "insulation" surrounding more active cells in the system.

Then there are "ordinary transmission" cell states. These are states which direct their activity in each of the four cardinal directions. Each of these may be in an excited or quiescent mode, so there is a total of eight different kinds of ordinary transmission states. In addition, there are eight "special transmission states," similar to the ordinary states in that they also point in each of the cardinal directions and can be in excited or quiescent modes. The two basic kinds of transmission states — ordinary and special — differ in that the primary intended role of ordinary transmission states is the routing of informational signals, whereas the primary role of special states is to inject transforming signals into cell locations and thereby convert "U" cells into active elements (or, if need be, convert active elements back into "U" cells).

The system also has four "confluent" states. These are activated if they receive signals from all cells in their neighborhood which are directed toward them. If activation occurs, then after two moments of time they emit signals outward toward any cell in their neighborhood

---

** Konrad Zuse is sometimes credited[323] with originating the concept of cellular automata.*

*** In September 1952, von Neumann was busy working on his cellular model. At first he conceived of his device as three-dimensional. To investigate this device, Goldstine[302] reports that von Neumann bought the largest box of Tinker Toys to be had. "I recall with glee his putting together these pieces to build up his cells," reports Goldstine. "He discussed the work with Bigelow and me, and we were able to indicate to him how the model could be achieved two-dimensionally. He thereupon gave his toys to Oskar Morgenstern's little boy Karl."*

**** Note that while this is true for von Neumann's CA, it is not true for all CAs in general which may include non-cardinal direction neighbors and other sorts of neighborhood templates in the determination of their state.*

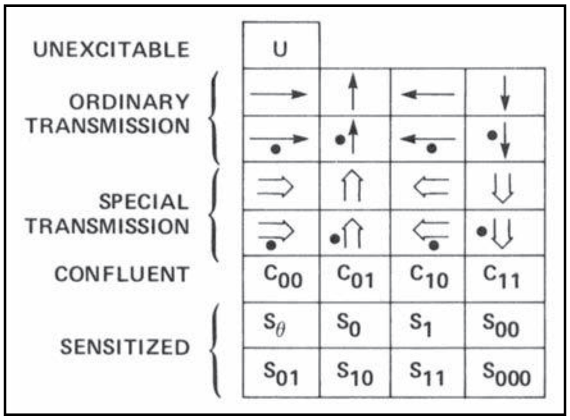


Figure 2.3. Twenty-nine states of von Neumann's cellular automata, from von Neumann.[4]

which does not have a transmission directed toward it. Thus, confluent cells can serve as AND gates, and as wire branching elements. Since they do not emit their output until two moments of time have elapsed, the confluent cells can also be employed to create time delays in the transmission of signals. The eight remaining cell states of the 29 originally employed by von Neumann are of less importance. These are temporary cell states which arise only as the operational states are being created from "U" cells.

Von Neumann first showed how to design a general purpose computing machine in his cell space system. He did this by showing the design of various basic organs — "pulsers" to emit any desired finite train of pulses upon activation, "periodic pulsers" to emit repeated trains of desired pulses after activation until signaled to stop, "decoders" to detect the presence of certain patterns of pulses, and the like. Using these organs, von Neumann developed a design for the control portion of a computing machine in one region of the cell space. He then showed how to organize an adjacent but indefinitely extendable portion of the cell space into a memory or information storage unit, which could be accessed by the control unit.

For the process of construction, von Neumann designed a construction unit (Figure 2.4), which, taking instructions from the memory unit, could send out a constructing arm (by creating an active pathway of transmission cells into a region of "U" cells) and at the end of the arm, convert "U" cells to the cell types specified in memory (Figure 2.5). He showed that this constructor could create any pattern of passive cells whatsoever. Thus, he had designed with mathematical rigor a universal constructor, relative to all possible passive configurations of cells in the cell space.

Since the parent machine itself can be created in passive form, it can make a duplicate of itself by the following process.[317] The parent machine is supplied initially with instructions to make a duplicate of its control, construction and memory units (the memory unit initially is empty). After it completes this major construction phase, the instructions call for the parent machine to make a copy of the instructions in its memory and to feed them into the memory unit of the newly constructed machine. Then the parent machine activates the heretofore passive offspring machine, and withdraws the constructing arm. At that moment the offspring is a duplicate, in all respects, of the parent at the time the original machine commenced its replicative activities.

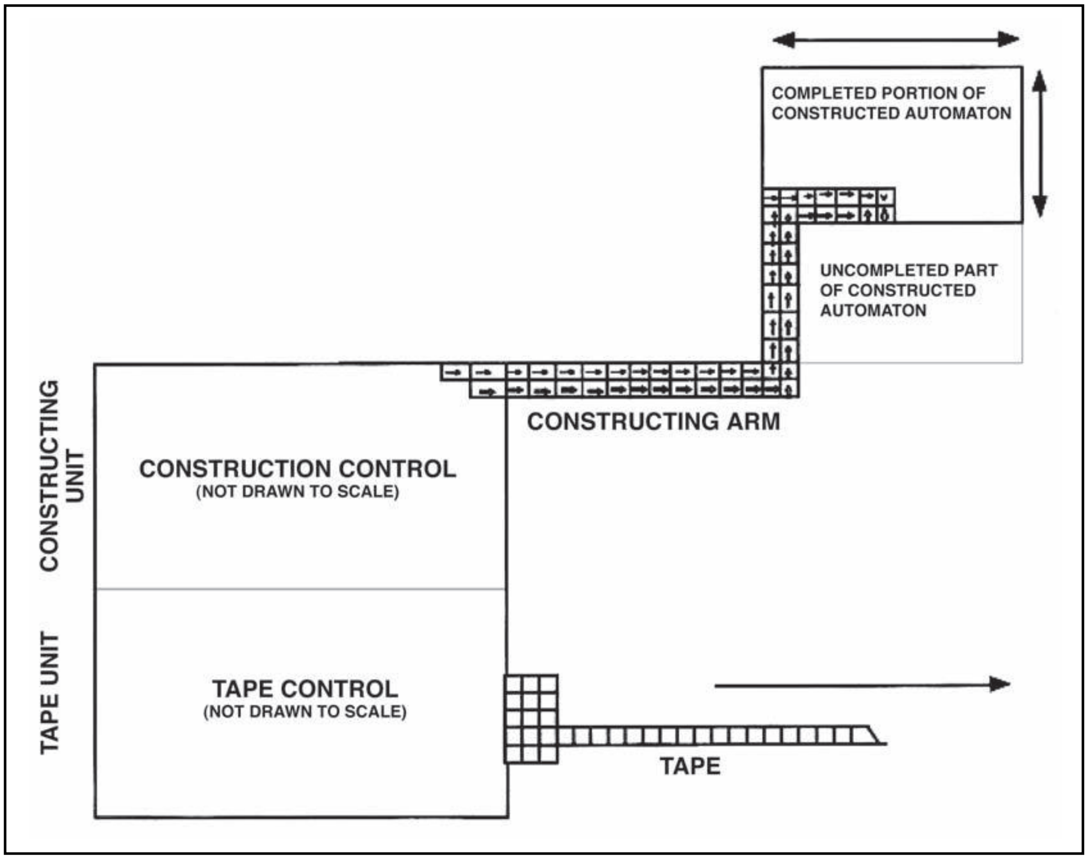


Figure 2.4. Universal construction in the cellular automata model of machine replication, from von Neumann.[4]

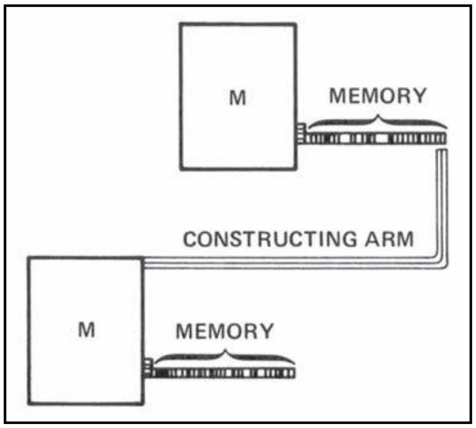


Figure 2.5. Universal construction arm builds the memory tape in the cellular automata model of machine replication, from von Neumann.[4]

Thus von Neumann was able to formally demonstrate[3] that his cellular model of machine replication possessed the several sufficient logical properties (Section 2.1.1) including logical universality, construction capability, and constructional universality,[324] thus enabling self-replication.

2.1.4 Limitations of von Neumann's Cellular Automaton Model

Although the 29-state von Neumann cellular array system (including a replicating device consisting of many millions of cells[372,373]) permits a more elegant mathematical approach to the problem of machine construction and self-replication, it is more difficult to envision an actual useful physical implementation of the process (compared, say, to the kinematic model of replication). The entire cell space enterprise proceeds in a highly constrained artificial environment, one which is very special despite some features relating in a general way to the natural world. For example, the movement of objects in space, a ubiquitous and familiar phenomenon in the real world, becomes a complex process of deletion of cell states at one location and re-creation of these states at some other location.

In von Neumann's model, there is an assumption of synchronous behavior throughout the system. All cells, no matter how distant, are subject to change of state at the same instant, a property which would be difficult to implement in any practical large cell space. Indeed, the requirement of a source of clocking pulses violates the array symmetry which makes the cell space notion an attractive object for mathematical treatment.

It is also very difficult to design machines of interest which can be embedded in von Neumann's cell array format. To make design and embedding easier, a higher-level machine design language would have to be created. It is likely that, rather than undertake that task, one would first redesign the underlying cell space properties to rid the system of the deficiencies already noted.

For instance, one might wish to introduce a new primitive cell state in the system to permit signals to cross without interference. A "wire-crossing" organ can be devised using only the original von Neumann primitive cell types, but this introduces an unnecessary complexity into the machine design process since the organ contains initially active cell states whose creation involves considerable extra care to avoid the propagation of spurious signals. This extra care is especially critical because the cell system, as von Neumann originally constituted it, is highly susceptible to signal errors. (He undoubtedly intended his probabilistic machine model to mitigate this sensitivity and fragility.)

Von Neumann's cell space system has very limited capacity to detect the states of cells. It has some capacity to detect states, for this is required in the operation of the memory unit. But a machine cannot analyze an arbitrary encountered cell to determine what state it is in, thus cannot "read" the states of an encountered machine. This inability severely restricts the capacity of von Neumann-type cell-space machines to repair other machines or to attempt self-repair. Such limitations also are evident in the construction process, where the constructing machine must assume that the region in which a new machine is to be created consists entirely of elementary quiescent cells. Should this not be the case, there is no systematic and complete way to detect it. A machine can send destruction signals into cells to reduce them to the quiescent form. Unfortunately, in some cases one must know the state of the cell ahead of time in order to determine what destructive signal must be sent to destroy it.

Finally, all machines that can be produced in von Neumann's cell space system are essentially information transactional devices. Even construction is, in this context, a form of information processing. Physical construction and material transformations can possibly be viewed as informational processes but, in a practical sense, the cell-space notion is far from providing a readily useful paradigm of actual manipulation and transformation of physical materials — that is, of kinematic self-replication.

2.1.5 Design for Nonevolvability

From the perhaps limited perspective of our desire to build "inherently safe" (Section 5.11) kinematic machine replicators that are incapable of evolving out of our control, Taylor[444] points out that von Neumann's work on self-replication concerned the question of how machines might be able to evolve increased complication in order to perform increasingly complex tasks. This is why von Neumann's design for a self-replicating machine had to be capable of universal construction, and why it could withstand some kinds of mutations. Von Neumann's architecture was designed specifically to allow for a possible increase in complexity (Section 2.1.1) and efficiency of machines by evolution,[2387] and it is quite clear that he was primarily interested in self-reproduction that could lead to open-ended evolution.[325] Noted von Neumann:[326] "Anyone who looks at living organisms knows perfectly well that they can produce other organisms like themselves.... Furthermore, it's equally evident that what goes on is actually one degree better than self-reproduction, for organisms appear to have gotten more elaborate in the course of time. Today's organisms are phylogenetically descended from others which were vastly simpler than they are, so much simpler, in fact, that it's inconceivable how any kind of description of the later, complex organism could have existed in the earlier one."

As to the nature of the information encoded on a self-description tape, Taylor[444] observes that von Neumann suggested "it is better not to use a description of the pieces and how they fit together, but rather a description of the consecutive steps to be used in building the automaton" (von Neumann,[318] p. 486). In other words, to optimize system auto-evolvability the information should be in the form of a developmental recipe rather than a blueprint (Section 5.1.9 (B5)). (The obvious corollary is that using blueprints rather than recipes can help to minimize auto-evolvability, which may be desirable in designing for public safety; Section 5.11.) The evolutionary advantages of this kind of genetic description have also been discussed by biologists such as Dawkins[327] (pp. 177-178, pp. 250-264) and Smith[264] (pp. 21-23), who note that from an evolutionary viewpoint, one of the most important features of the developmental approach is that it allows mutations on the genotype to have a wide range of magnitudes of phenotypic effect. For instance, mutations affecting the early developmental process can potentially lead to gross macroscopic changes in phenotype, whereas those affecting later stages can have the effect of "fine-tuning" particular structures.[444]

Thus it seems axiomatic that desirable artificial nanomachines which are capable only of "inherently safe" replication without the possibility of surviving mutation or of undergoing evolution should have a simpler, less-capable architecture than those proposed by von Neumann and by others who are interested primarily in modeling living processes which need the more-capable architectures. That is, it should be possible to abandon complete logical or constructional "universality" and still retain the ability to self-replicate, but without the ability to self-evolve (Section 5.1.9 (L)). Drexler[328] has also noted the brittle organization of mechanical-style replicating systems as compared to organic-style replicating systems, and concludes: "It seems that building a self-replicating molecular system based on nanomachinery does not entail building a system capable of evolution. Indeed, it seems that the latter would be a distinct and challenging goal."

2.2 Subsequent Work on Computational Models of Self-Replication

2.2.1 Cellular Automata Models of Self-Replication

Work on cell-space automata systems in the period following von Neumann's virtually unique[329,330] contributions has been both lively and extensive, and has taken many different research directions.[331-336,380] The underlying cell-space notion of an homogeneous medium with a local transition function that determines global properties has been employed in numerous modeling and simulation projects. For example, weather simulations use the idea of connected cells, the changes of each cell state described by a set of differential equations. Studies of the flow of excitation in heart tissue, the dispersal of medicinal drugs, pattern recognition and cryptography,[337] autocatalysis,[338] prion infection,[1736] biological cell function,[339-342] and even the origin of life[343,344] all have employed the cell-space concept. Cell spaces also have been investigated as abstract mathematical objects where, for instance, one tries to determine whether from every mathematical pattern all other patterns can be attained, and whether there are some patterns not attainable at all by means of the transition function, and various other specialized questions. Even by the late 1960s, the investigation of cell-space systems as abstract mathematical entities or as vehicles for spatial modeling and simulation (especially cell-space imaging applications[345]) was already vigorous and prolific. Work on cellular automata has been reported under many other names including iterative arrays, tessellation automata, cellular spaces,[382] modular arrays, and polyautomata.[346]

Much work in cellular automata has attempted to carry forth the von Neumann program of cell machine construction and self-replication. For instance, Codd[347] recapitulated the von Neumann results in a simpler cell space requiring only 8 states rather than 29, using "sheathed loops"[358-362] surrounding the replicating device (believed at the time to be essential for indicating growth direction and for discriminating right from left[348]), but his device required about 100,000,000 cells[372,373] (later reduced to 94,794 cells by Devore[349]). This produced a machine design recognizably closer to that of present-day computing machines. Myhill,[350] trying to mitigate the artificiality of the indefinitely extended pre-existing cell space, designed a system in which componentry was drawn into a cell-grid system and was then employed as machine constituents somewhat as biological cell constituents might be drawn through a membrane to be used at an intracellular work site. Myhill[351] and Ostrand[352] generalized von Neumann's basic result to other configurations and higher dimensional cellular spaces. Arbib,[354] attempting to make the movement of cell machines a less cumbersome matter, designed a cell-space system in which cells and blocks of cells might be joined together by a "welding" operation, thus becoming rigid "co-moving" configurations "as if held together by chemical bonds." Moore[353] established theoretical upper bounds on the rapidity of growth of a population of self-replicating configurations, and many others[200,201,357-380] have continued to examine various fundamental definitional issues of replicating cellular automata, and to explore fault-tolerant self-replicating CA structures.[385,386]

How simple can a self-replicating cellular automaton be? Reggia et al[348] point out that although the von Neumann and Codd structures do self-replicate, they generally consist of tens of thousands or millions of components or active cells and as a result have never actually been completely simulated computationally[387,388] because of their tremendous size and complexity.* In 1970, Smith[389] and Banks[364] introduced additional simplifications to the cell-space notion, showing that the von Neumann program could be recapitulated in underlying cell spaces of an extremely elementary sort. Indeed, the "Game of Life" created by Conway[390-396] is a cell-space system which, despite its very simple transition rules, has been claimed to be capable of expressing both universal computation and construction. The game involves a checkerboard cell array with cells in one of two states, "0" or "1." A point whose state is "0" will change to state "1" if exactly three of its eight neighbors are in state "1." A point whose state is "1" will remain in that state if two or three of its neighbors are also in state "1." In all other cases, the state becomes or remains "0." In the Fredkin cell space defined by the "two-state Parity rule" each cell goes to "1" if an odd number of neighbors are "1" and goes to "0" if an even number of neighbors are "1" — the Fredkin Parity rule will then make copy after copy of whatever starting pattern you give it, with the number of cycles to obtain a replica depending upon the seed configuration (the larger the seed, the longer replication takes).[397,398]

A breakthrough in cellular automata theory came in 1984, when Langton[359] realized that the capacity for universal construction is a sufficient but not necessary condition for self-replication,** noting that natural biological systems are not capable of universal construction either. He set out to find the logical organization of the smallest possible structure that could accomplish self-replication (and

---

** Umberto Pesavento, a young Italian high school student and software prodigy, developed a simulation[388] of von Neumann's entire universal constructor, under the direction of Renato Nobili who provided "the graphic environment of the program and all ideas on how to pursue the goal".[399] The computing power available did not allow Pesavento to simulate either the entire self-replication process (the length of the memory tape needed to describe the automaton would have required too large an array to execute in a reasonable period of time) or the Turing machine necessary to implement the universal computer, but he was able to demonstrate the full functionality of the constructor.[308] For example, according to Tim Hutton.[399] "If you wrap the memory around, [the program] will fit in a reasonable amount of space. The problem comes when executing the CA, since the number of active cells grows hugely. Umberto said this to me: 'Are you trying to run a full self-reproduction? The tape size should not be a problem in the geometrical sense but sending information up and down the arm that reads the tape may be slow for a tape that long.' Of course, with a highly parallel hardware implementation of the CA this would not be a problem, but for serial implementations, even those which take advantage of the fact that only active cells need to be processed, the computation time is too great. I left the machine running on my 1.7GHz machine for a week and it went from thousands of iterations per second down to one iteration per five seconds, having only got less than half way down the tape. There are ways of simulating the tape to avoid these problems but they require treating some cells differently from others, which is unsatisfactory."*

*** In 1969-1971, Alvy Ray Smith provided a proof,[417] based on the famous Recursion Theorem of recursive function theory, that computational universality alone will suffice for nontrivial machine replication (as cellular automata).[346] Von Neumann required both computational universality and construction universality in his self-reproducing machines.*

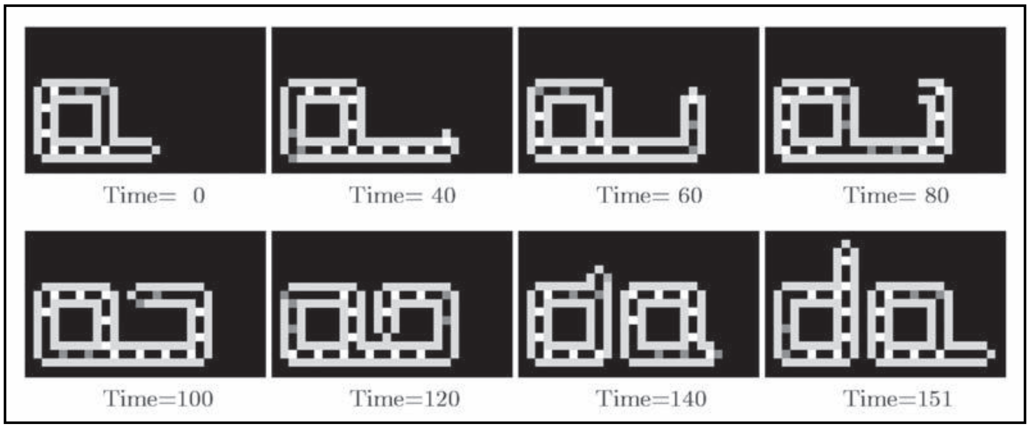


Figure 2.6. Self-replication of Langton's SR loop. (courtesy of Sayama[403-406])

nothing else). Langton discovered that looplike storage devices, previously present only as modules within earlier self-replicating cell automata designs, could be programmed to replicate on their own (Figure 2.6). These devices (e.g., an 86-cell loop embedded in an 8-state 2-D cellular space) typically consist, first, of a string of components that circulate around a rectangle, and, second, a construction arm that protrudes from a corner of the rectangle into the surrounding cellular space.[400] The instructions are used twice, once for translation and again for transcription. In 1989, Byl[362] discovered a much smaller 12-cell self-replicating loop embedded in a 6-state cellular space, and in 1993 Reggia et al[348] found an even smaller "unsheathed" replicating loop, an information pattern comprising only 5 cells embedded in a 6-state space that can replicate in just 17 cycles. This simple replicator was demonstrated in 2001 using chess pieces on a chess board.[190]

Chou and Reggia[401,402] and Pargellis[468] observe that a selected cellular automaton grid "primordial soup" will spontaneously give rise to small self-replicating structures without seeding, and that cellular automata can readily support evolution.[3,403-406] Simple self-replicating loops for reversible cellular automata (e.g., following the pattern of a retractile cascade in a reversible computer[407]) have been investigated by Morita and Imai.[408-412] Others continue to explore interesting extensions of these loops,[403-406,413] including self-replication[414] and evolution[386] implemented in asynchronous cellular automata. For example, Mange et al[415,416] present a generalized self-replicating loop called the "Tom Thumb algorithm" which is endowed with universal construction and which verifies the six criteria of autopoietic machines (Section 5.1).

Self-replicating computer programs (often called quines[418,425]) have been written in more than 50 different software languages.* [419-427,473] Various other forms of self-replicating software have served as the basis for games such as "Core Wars",[428-432] Hauser and Buckley's "Apple Worm",[429] Wator,[438] Flibs,[439] and many** artificial life simulations[372,373,440-485] including most notably Nils Barricelli's symbioorganisms[445-447] and Thomas Ray's "Tierra" virtual organisms,[442] digital worms,[432-437] computer viruses,*** [486-495] and studies of the "biology" of digital organisms by Adami and others.[503-513] (Adami[503,504] notes that "evolving, self-replicating programs behave just like evolving, self-replicating molecules, and their dynamics are indeed well described by Eigen's theory (Section 4.1.6) of macromolecular evolution" — although computer viruses do not obey the same rules as biological viruses, such as Koch's Postulates).[514]

** Merkle prefers to quote the following example of the shortest known (one-line) C program that prints out an exact copy of itself without any user input, originally published by professional C programmers Burger, Brill and Machi*[422] *in 1980, who crowed that their tiny self-replicating program is a mere 101 bytes in length:*

```
main(){char q=34,n=10,*a="main(){char q=34,n=10,*a=%c%s%c;printf(a,q,a,q,n);}%c";printf(a,q,a,q,n);}
```

Written in English, these instructions would read as follows:

Print the following statement twice, the second time in quotes:
"Print the following statement twice, the second time in quotes:"

As a former aficionado of the now ancient Commodore PET/CBM line of personal computers, Freitas is pleased to pass along the 1981 observation of then-ninth-grade high-school student William Sommerfeld[424] *that the simplest known self-replicating program, executable on the PET, technically requires only 2 bytes of storage because of the way the PET BASIC interpreter stores instructions, and may be written simply as: 1 LIST*

*** Some artificial life simulations don't involve self-replicating software directly, but simply data that are copied by an "external" program, as in the case of genetic algorithms.*

**** As of 16 May 2003, there were 63,791 computer viruses recognized and catalogued by Norton AntiVirus.*[515] *According to Harold Thimbleby,*[516] *"a* ***computer virus*** *is a piece of program code that attaches copies of itself to other programs, incorporating itself into them so that the modified programs, while still possibly performing their intended function, surreptitiously do other things. Programs so corrupted seek others to which to attach the virus, and so the 'infection' spreads. Successful viruses lie low until they have thoroughly infiltrated the system, and only reveal their presence when they cause damage. The effect of a virus is rarely traceable back to its originator, so viruses make attractive weapons for vandals. Computer viruses generally work by altering files that contain otherwise harmless programs. This is infection. When an infected program is invoked, it seeks other programs stored in files to which it has write permission, and infects them by modifying the files to include a copy of itself (replication) and inserting an instruction to branch to that code at the old program's starting point. Then the virus starts up the original program so that the user is unaware of its intervention. The exact details vary from virus to virus."*

Thimbleby[516] *defines other kinds of malicious software as follows: "A* ***logic bomb*** *or time bomb is a destructive program activated by a certain combination of circumstances, or on a certain date. A* ***Trojan horse*** *is any bug inserted into a computer program that takes advantage of the trusted status of its host by surreptitiously performing unintended functions. A* ***worm*** *is a distributed program that invades computers on a network. It consists of several processes or 'segments' that keep in touch through the network; when one is lost (e.g., by a server being rebooted), the others conspire to replace it on another server — they search for an 'idle' server and load it with copies of themselves. Like viruses, worms spread by replication; unlike them, they may run as independent processes rather than as part of a host program."*

Thimbleby[516] *briefly recounts the prehistory of the computer virus as follows: "In 1962, V.A. Vyssotsky, a researcher at Bell Telephone Laboratories (New Jersey), devised a game called Darwin, played on an IBM 7090 computer. The object of the game was survival, for 'species' of programs to fight it out in an arena set up in the 7090's memory. Successful programs would be able to make more copies of themselves, and perhaps go on to take over the entire arena. The idea was taken up ten years later*[517] *and converted to run on other computers. Within the somewhat arbitrary rules of the game, Doug McIlroy invented what he called a virus: an unkillable organism that could still fight. The idea of a maliciously self-propagating computer program originated in Gerrold's 1972 novel* When Harlie Was One,[518] *in which a program called telephone numbers at random until it found other computers into which it could spread. Worms were also presaged in science fiction, by Brunner's 1975 novel* The Shockwave Rider;[519] *the first published report of a worm program, done in 1982 by Shoch and Hupp*[433] *as an experiment in distributed computing, included a quotation from this book."*

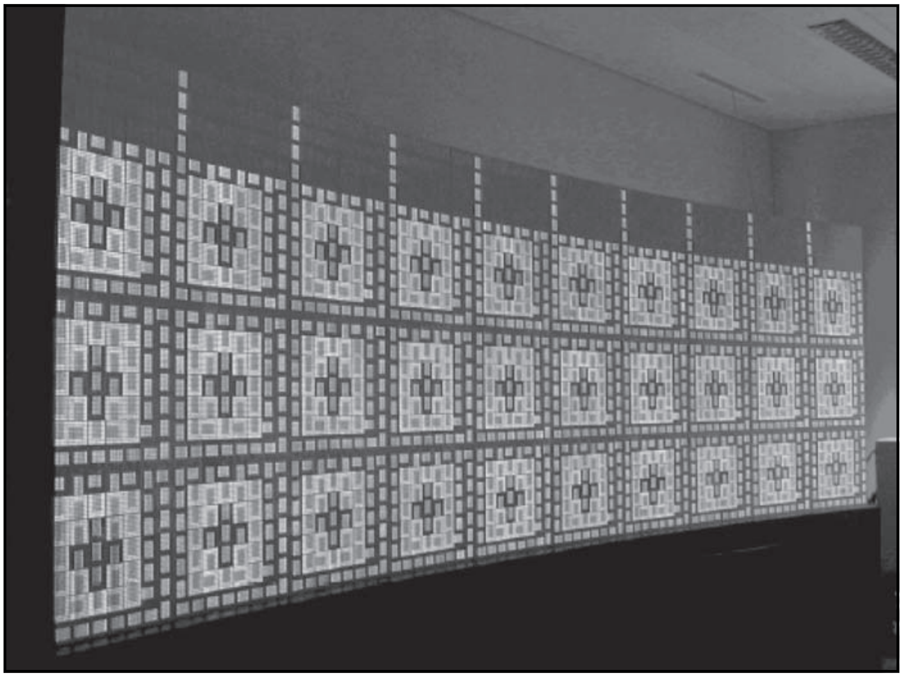


Figure 2.7. BioWall implementation showing genotypic data path and phenotypic representation of Swiss flag. (photograph by A. Badertscher, courtesy of Daniel Mange[415])

Still others have demonstrated, for example, the spontaneous emergence of self-replicating LISP programs,[372,373,520,521] although Koza[372,373] estimates that "the probability of creating a self-reproducing computer program entirely at random must be exceedingly small."* There are also mimetic replicators[522] such as ideas, rumors,** jokes, advertisements as in "viral marketing",[523] sentences,[524] musical tunes,[602] or poems,*** collectively called "memes," that spread throughout a population by being copied again and again as people pass them on to their friends, thus replicating themselves on the social substrate of active human minds.[525,526] Thus memes may be regarded as a species of self-replicating automata.

Although cellular automata replicators often do not readily lend themselves to physical realization, physical arrays of parallel processors such as the field-programmable gate array (FPGA) and other pieces of specialized hardware[529] have been built that exhibit properties such as self-repair (healing) and self-replication.[530] A good example is the "Embryonics project"[531-542] — e.g., the "Bio Wall" (Figure 2.7) unveiled in February 2002 by the Logical Systems Laboratory of the Swiss Federal Institute of Technology Lausanne (EPFL or Ecole Polytechnique Fédérale de Lausanne)[543-546] for fault-tolerant computing.[547] The main goal of the Embryonics project[540] is to implement, in an integrated circuit, a system inspired by the development of multicellular organisms and capable of self-test and self-repair. In Embryonics, an artificial organism (a group of artificial cells that executes a given task) is realized by a set of cells distributed at the nodes of a regular two-dimensional grid. Each cell contains a small processor coupled with a memory used to store the program (identical for all the cells) that represents the organism's genome. In the organism, each cell realizes a unique function, defined by a subprogram, called the gene, which is a part of the genome. The gene to be executed in a cell is selected depending on the cell's position within the organism as defined by a set of X and Y coordinates.

The first kind of self-replication in Embryonics systems is that of the organism. An artificial organism is capable of replicating itself when there is enough free space in the silicon circuit to contain the new daughter organism and if the calculation of the coordinates produces a cycle. In fact, as each cell is configured with the same information (the genome), the repetition of the vertical coordinate pattern causes the repetition of the same pattern of genes and therefore also, in a sufficiently large array, the self-replication of the organism for any number of specimens in the X and/or Y axes.

There is also a second replication process, corresponding to the cellular division process in biological entities, that is used to put in place the initial array of cells that will then be differentiated to obtain the organism. The need to build cells of different size and structure depending on the application naturally led to the use of programmable logic (FPGAs) as a physical substrate. Each of the computational elements of the Embryonics FPGA can thus be seen as "molecules" assembled in a precise configuration to form a cell. Since all cells are identical, the development process is analogous to the replication of this configuration for as many iterations as there are cells in the organism.

To implement this replication, Embryonics splits the process into two phases: (1) the structural phase, where a "skeleton" is created in order to divide the physical space in a collection of groups of molecules which are empty cells; and (2) the configuration phase, where

---

** Koza[372] estimates that the probability of finding of the classical cellular automata programs in a blind random search as follows:*

Proposed Models	*Number of Components*	*Probability of Positive Search*
Codd's eight-state automata[347]	10^8 *cells*	$\sim 10^{-9,000,000}$
Von Neumann's 29-state automata	*>200,000 cells*	$>10^{-292,480}$
Devore's version of Codd[349]	*94,794 cells*	$10^{-85,315}$
Ray's handwritten Tierra program[442]	*80 lines of code*	10^{-120}
Langton's simple CA program[358-361]	*100 cells*	10^{-91}
Ray's evolved Tierra program	*22 lines assembly code*	10^{-33}

*** An amusing example:[527] "In the reformatory at Caserta, Italy, as guards watched a movie, five youthful prisoners escaped. The movie the guards were watching was about guards who watched a movie while youthful prisoners escaped."*

**** There is a short story written by David Moser[528] in which every sentence in the story is self-referential.*

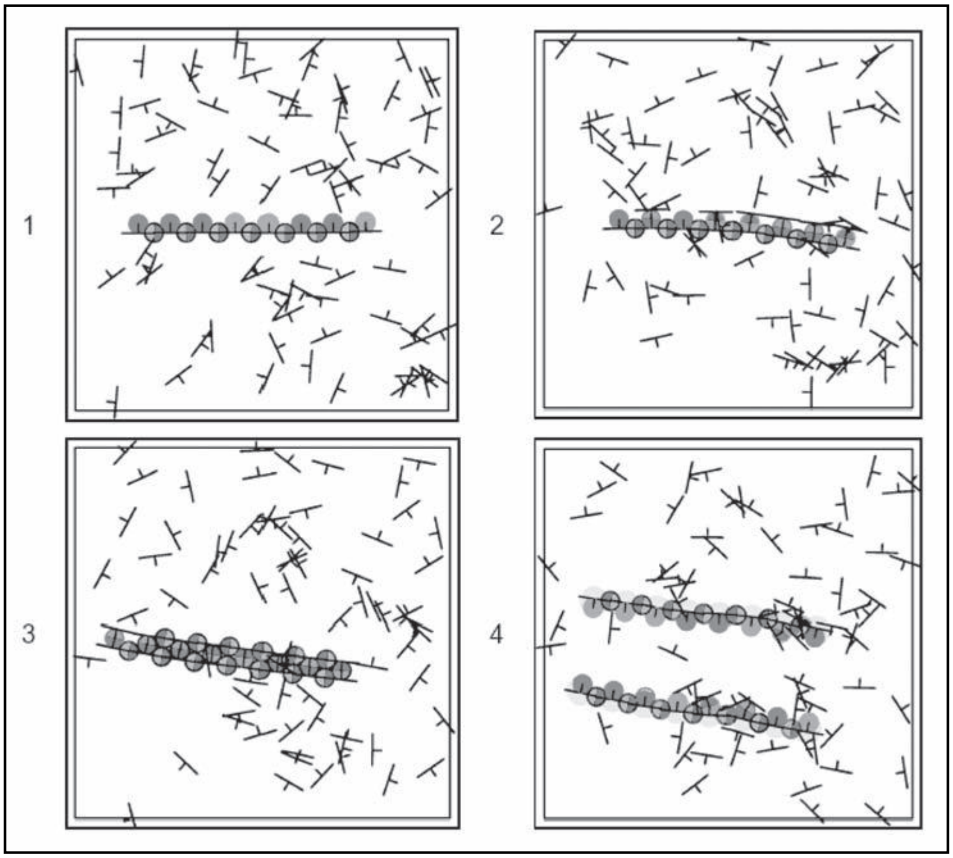


Figure 2.8. Typical run of JohnnyVon program with a seed strand of 8 codons and a soup of 80 free codons.[481] (© 2003 NRC; permission to use copyright material courtesy of Peter Turney)

the configuration is sent in parallel into all the empty cells created during the structural phase. The structural phase is implemented by a small cellular automaton, integrated into the molecular grid, capable of transforming a one-dimensional string of states (analogous to a configuration bitstream stored in a memory chip) into a two-dimensional structure (i.e., the blocks that will host the cells). This replication process is quite different from biological cellular division because all cells are created in parallel. A new approach,[415] designed to be integrated with Embryonics, implements a cellular division much closer to real biology.

In 2000, an FPGA embodying a single 29-state cell of von Neumann's original cellular automata model was implemented in hardware by Beuchat and Haenni.[412] The Cell Matrix™ [550] architecture represents another physical architecture that could support cell automata self-replication and self-organization, and other novel electronics architectures based on cellular automata have been discussed.[548,549] It may even be possible to self-assemble FPGAs.[550-552]

Wilke and Adami[553] summarize the current state of their field as follows: "The main focus of digital life research is a sort of comparative biology, which attempts to extricate those aspects of simple living systems that are germane to the type of chemistry used, from those that are not.[554] Additionally, digital life can help to refine mathematical theories and aid in developing and quickly testing new hypotheses about ecological and evolutionary processes. Current state-of-the-art digital life research platforms create essentially single-niche ecosystems, and the dynamics that unfold are similar to bacterial or viral evolution in chemostats. However, more complex ecosystem structures can be realized within the paradigm of self-replicating computer programs, and we can expect research to increase in this area. Apart from their usefulness as a tool of understanding evolution in general, it is important to study the biology of artificial life forms in their own right. Recently, Lipson and Pollack[927] showed that the principles of simple self-replicating robots are within reach of current technology (Section 3.20). Eventually, such robots, and the software that directs them, might evolve without human interaction, at which point they would become part of the ecosystem in which we live."

It is worth noting that robots cannot really be considered part of the ecosystem unless they can forage for raw materials (in said ecosystem) as well as replicate themselves. Such an ability to forage is unlikely to be developed, deployed, or even to be made legal because it would violate the Foresight Guidelines[271] and could threaten public safety (Section 5.11).

2.2.2 Computational Modeling with Continuous Space and Virtual Physics

There is a long history of work on self-replicating cellular automata (Sections 2.1.3 and 2.2.1) which are discrete, finite-state, abstract machines that replicate in a tessellated (fixed-grid) universe, like the squares on a checkerboard. But some researchers believe that continuous models may have many advantages over discrete models, such as increased realism (because the real physical world is continuous) and robustness. (The distinction between "discrete" and "continuous" comes from mathematics, wherein, for example, the integers are discrete but the real numbers are continuous.) Following this idea, Smith, Ewaschuk and Turney[481] have recently developed a computer model called "JohnnyVon" which consists of self-replicating mobile automata that move around in a continuous two-dimensional space — a virtual "soup" of simulated fluid. The particles are subject to simulated laws of artificial physics including inertia, Brownian motion, pseudo-viscosity, and spring-like attractive and repulsive forces. The choice of a 2-D space for the initial work was a tradeoff between computational complexity and realism, since 2-D is more realistic than 1-D yet is easier to compute than a 3-D model (the present 2-D simulation runs on a desktop computer).

The automata particles or "codons" (each carrying one bit of information) can encode arbitrary bit strings and comprise T-shaped virtual objects that possess both attractive and repulsive fields. These objects form chains and the chains replicate, much like DNA replicates (Figure 2.8). The initial seed pattern can be arbitrary. In nature, a seed pattern such as a particular string of DNA can replicate, but it can also encode a plan for building something such as a protein, cell, or organism. In the original implementation of JohnnyVon, seed patterns can only replicate; they do not encode plans for building things. That is, they are all genotype, no phenotype.

Consistent with the Foresight Guidelines (Section 5.11), JohnnyVon's design does include a built-in safety factor: it can only assemble things using the codons as components. The system includes no ability to create new codons out of raw materials found in the environment. New codons must be created by some other process — in a physical implementation, this would presumably require some type of external traditional manufacturing process such as lithography. Notes Turney:[555] "It's as if we had discovered a way to make Lego bricks self-assemble into finished structures. Once all the loose Lego bricks are used up, the process necessarily halts."

However, because the researchers are interested in investigating aspects of living systems as opposed to manufacturing systems, their approach incorporates several capabilities that might diminish the "inherent safety" (Section 5.11) of the replication. For example, even without a starting seed, self-replicating patterns can arise spontaneously. In other experiments that do use a seed pattern, JohnnyVon demonstrates four properties required for evolution: (1) patterns that replicate, along with (2) characteristics that are inherited, along with (3) mutation and (4) a selection process that favors the replication of some patterns over others, based on their inherited characteristics.[555] Evolvability (Section 5.1.9 (L)) is an undesirable property of physical replicators intended to perform their functions safely in the physical world, so additional safeguards to forestall evolution may be required before JohnnyVon should be developed into a robust physical implementation.

The next step in this research — to add phenotypes, ongoing work still unpublished as of 2003 — includes a new software implementation[555] wherein a strand replicates a fixed number of times and then ceases all further replication. After ceasing replication, the strand enters a new state in which it becomes a "phenotype" (a "body") rather than a "genotype" (a template for replication). In this new "phenotype" state, the strand is no longer straight; it folds into a shape that is determined by the pattern of 0s and 1s that it encodes, intended to be analogous to the way that proteins fold in real life. The angles between adjacent codons in the strand depend on whether a 0 codon is adjacent to a 1 codon, two 0 codons are adjacent, or two 1 codons are adjacent. The strand can be bent into an arbitrary shape by encoding the appropriate sequence of 0s and 1s. Turney[555] explains: "The obvious approach to 'productive replicators' (Section 5.1.9) is to have two types of entities: replicating entities (genotypes) and final product entities (phenotypes). Instead, we have a single entity that switches roles over time (genotype as a child, phenotype as an adult) (cf. Figure 3.39). This is a very efficient approach to manufacturing, since all of the entities eventually become part of the final product. There is no residue of non-functional replicating entities that must be filtered out of the final product."

2.3 Alternative Models of Machine Replication

Subsequent theoretical work explicitly derived from von Neumann's research effort has focused mainly on the molecular biological analogies that can be drawn. For instance, Laing[557-563] employs a hybrid cellular-kinematic model (Section 3.8) of machine construction and shows that neither existing natural nor artificial machines need be bound to follow the "classical" replication paradigm. In the classical paradigm, a program (DNA in living systems) is first interpreted to construct a machine (ribosomes and the other molecular machinery of a cell) and then is read a second time to make a copy of the program for insertion into the newly constructed duplicate machine (DNA replication in living cells). The principal contribution of Laing is to suggest reproductive strategies other than direct analogs to the known biological process. In this new conception, a machine is able to identify all of the components of which machine systems are comprised (not merely a subset as in the von Neumann cell system), and can access all of an existing machine structure without requiring dismantling of the system (as would be required in the von Neumann model). For example,[558] to produce offspring a parent could begin with a description, or with a set of instructions for construction, or with a set of instructions for a description, or with a description of a set of instructions for a construction, or with a description of a set of instructions for a description, or with a constructor of a describer of a set of instructions, etc. Once these and other similar concepts are brought to bear on the problems of machine reproduction, many alternative reproduction strategies immediately become apparent — a selected few of which are briefly reviewed below.

2.3.1 Simplified von Neumann Automaton Replication

Von Neumann's automata replicative process closely mirrors the biological one. In the original model, instructions exist in two copies. One of the copies is read and acted upon to construct another machine, but without instructions. The second copy is then read and copied twice, and this double copy is inserted into the passive constructed offspring machine which is then turned on and released, thus completing the act of replication. There is no logical necessity for having two sets of identical instructions. Von Neumann employed two copies of the instructions because it eliminated the criticism that the instructions might, in the first (construction) phase, become corrupted and so not be able to transmit a true version for the use of offspring machine. Another solution is to provide the machine proper with an automatic "wired-in" copy routine which the program calls for at the proper time.

2.3.2 Von Neumann Automaton Replication with Diversification

Consider a single instruction tape, and a constructor machine which reads the instructions once to build the offspring machine and again to make a copy of the instructions for the offspring machine. Notice that although the instructions available to the system yield a duplicate of the original system, this need not always be the case. Machines may read and interpret instructions without knowing what they are being called upon to do. The instructions might call for some computational, constructional, or program-copying activities. The machine can be programmed to make machines unlike itself, and can give these "unnatural" offspring copies of the instructions which were employed in their manufacture. If the offspring are also equipped to read and follow instructions, and if they have a constructional capability, their offspring in turn would be replicas of themselves — which might not resemble their "grandparent" machine at all. Thus, an original construction machine can follow instructions to make an indefinitely large number of diverse machines, that are like or unlike themselves, capable or not capable of constructing, replicating, and so forth.[564]

2.3.3 Thatcher's Variant: Inferring Structure

Thatcher[565] showed that a machine need not have an explicit construction program made available to it initially in order to create a duplicate of itself. First, it is sufficient that a machine can secure a description of itself (in place of instructions) if the machine is equipped with the capacity to read the description and convert this into the necessary constructive actions. Second, Thatcher showed that such a machine need not have its description loaded beforehand into its accessible memory organ. Instead, the machine has a partial self-description hard-wired into itself in the form of circuits which, when stimulated, make the description available to the machine in its accessible memory organ. These data describe all of the machine except the hardwired part which was stimulated to emit the description in the first place. The problem then, for the machine, is to obtain the description of this hidden part of itself. Lee[566] and Thatcher[567] showed that this section of the device can be constructed in such a simple fashion that the system can infer how this part must have been constructed merely by examining the consequences of its actions (e.g., the partial description that it produced). After inferring the nature of this hidden part of itself, the machine possesses a complete self description and can then follow von Neumann's paradigm for replication.

The principal practical significance of this result is to remind the designer that the information required for machine construction (whether replication or otherwise) need not be in the form of instructions for constructions but can instead be in the form of a description. Moreover, the description need not even reside in an accessible organ such as memory registers but may be embedded in "inaccessible" hardware. The hypothetical infinite regress (Chapter 1) likewise is shown to be baseless — it is possible for a machine to have within itself only a part of its own description, and from this to infer the rest. However, there may be an elevated risk of evolvability using this scheme.

Case[568] offers the metaphor of a transparent self-replicating robot that examines itself in a mirror, writes down its own description on a blackboard from what it sees in the mirror, and then uses the description written on the blackboard to build a copy of itself. Explains Case: "Note that the robot's self copy is projected *externally* to the robot itself. In this way infinite regress is not required for the robot to have *complete* (low level) self-knowledge." Others have also examined the issue of machine self-reference.[569-571]

2.3.4 Replication by Component Analysis

In von Neumann's cellular model, an embedded machine cannot send out an inspection arm to an encountered machine to identify all of its states. However, the cell space system could be redesigned to permit this. In such a system, an analyzing machine could examine an encountered passive machine and identify the type and location of all its cell automata. (The analyzer might of course have to penetrate the machine, thus altering its automaton states, so the inspecting arm would have to send out appropriate restoration construction signals.)

In von Neumann's kinematic model, a machine ostensibly could identify all parts of the system and thus determine the type and location of all components. This opens the possibility that a machine system might, for example, replicate essentially two machines — one active, the other passive (or able to assume passivity under a signal from the active machine). This possibility and others have been explored by Laing[557-563] in a series of papers presenting alternative replicative strategies which include the following:

a. **Unilateral Reverse Engineering**. Beginning with two identical machines, one active and one passive, the active machine reads the passive machine twice, producing one active and one passive machine, thus completing replication.

b. **Cooperative Reverse Engineering**. Beginning with two machines (not necessarily identical) one machine reads the second, and makes a duplicate of it. Then the second reads the first, and makes a duplicate of it, active and passive status being exchanged. This result can be generalized to multiple machines.[564]

c. **Inferential Reverse Engineering**. By combining the capacity of machines to read machines with the Thatcher result, one can hardwire a machine to construct a second machine which is a duplicate of the original except for the hardwired part which produced the second machine. The original machine then reads the newly constructed partial duplicate, and infers what the missing hardwired part must be. The original machine then constructs the missing part, completing the replicative process. This result also explicitly confronts and overcomes the "necessary machine degeneracy" criticism of automata self-replication.

2.3.5 Machine Replication without Description

In the machine replication schemes examined thus far, some arbitrary part of the machine which cannot be inferred is always made explicitly available in memory initially, or is implicitly made available in memory or for inspection by means of an internal wired-in memory, also not directly accessible. Laing[560] showed that even this wired-in description is not necessary. In effect, a machine can carry out a self-inspection which can yield a description which in turn can be made available to the machine in constructing a duplicate of itself.

The process begins with a wired-in construction routine which produces a semiautonomous analyzer machine. This analyzer moves over the original machine and identifies the type and location of its componentry. This is reported back to the original machine, which uses this information to make a duplicate of itself. Thus, though it may be that a part of a machine "may not comprehend the whole" in a single cognitive act, a part of a machine can examine in serial fashion the whole machine, and in time can make this information available to the machine for purposes of replication. In other words, if the structure of a parent automaton can be inspected and thus can serve as the blueprint for its offspring, then the system can transfer the parent's information to its offspring.

In the example of self-inspection shown in Figure 2.9, the initial automaton configuration is (D) = general-purpose constructor, (C) = optional substring, (B) = destroyer, and (A) = special-purpose constructor. According to Laing,[561] the process proceeds as follows:

i. (A) constructs (1) analyzer, (2) inferrer, (3) general-purpose constructor, and (4) destroyer.
ii. analyzer (1) identifies the primitives of (A), (B), (C), and (D); inferrer (2) uses this information to instruct general-purpose constructor (3) to produce (E), the emitter of a description of (A), (B), (C), and (D).
iii. the emitter (E) produces the description (5) of (A), (B), (C), and (D).
iv. destroyer (4) removes the emitter (E)
v. destroyer (B) removes (1), (2), (3), and (4).
vi. constructor (D), using description (5), produces (A)', (B)', (C)', and (D)'.
vii. destroyer (B) removes description (5).

Self-replication of the original automaton is now complete, solely via an examination of its structure. "Whatever properties the original possessed at the time of reproduction are now recreated in the offspring ... a model of reproduction in which the use of a distinct description is not central to the process and in which any acquired characteristics of the original parent string would be reproduced in the offspring string.[561] In other variants of this system, "the information acquired by the new analysis string need not be temporarily stored in the description and emitter of a description, but is acted upon as it is acquired. Machine reproduction by self-inspection without creation and destruction of auxiliary strings can [also] be exhibited in the kinematic system."

Replication by self-inspection[560-563,374] can allow the description of the machine which is to be replicated (i.e., the "phenome") to be dynamically constructed concomitantly with its interpretation. Laing[561] notes that the capacity of a system generally to explore its own structure and to produce a complete description of itself for its own perusal and use (e.g., to generate and evaluate behavioral options open to it) seems to be an advantageous capacity not exhibited anywhere in naturally occurring systems. Of course, self-inspection becomes increasingly difficult as replicating systems grow in complexity,[2382] and also when the system being inspected cannot enter a state of stasis.[572] As Friedman[573] points out, "self-inspection might be practical for cellular automata — where the machine is entirely within the information domain — or with von Neumann's 'sea of parts' — where all the subassemblies can be identified merely by reading a part number or a serial number. [But] with the 'moles of parts' that are claimed for MNT [molecular nanotechnology], I can't conceive how the self-inspecting sensors can gain access to the internal structure — which is most of the machine to be self-replicated."

Peter Silcox[574] also warns that self-replication by self-inspection is potentially evolutionary, since self-inspection provides a ready means by which phenotypic variation can become incorporated into future generations of the replicator. If one such random variation happened to disable a subsystem whose primary function was to prevent evolution, the subsequent line of replicators could become unconstrained in their replicative behaviors, violating our desire for inherently safe replication. This implies that replication controls on self-inspecting replicators should be distributed in multiple sites throughout the machine, such that the loss of function or outright omission of these controls during construction of daughter machines will result in nonfunctional daughter machines.

Interestingly, Chirikjian[1297] has proposed a partial "replication without description" approach as a way to save mass, and hence transportation costs, in the context of a lunar self-replicating factory whose initial "seed" must be sent from Earth. A crucial subsystem in Chirikjian's hypothetical factory (Sections 3.24 and 3.25.2) is an electromagnetic railgun to widely disperse replicated daughter units across the lunar surface. However, the components for even a single railgun in an initial seed factory would be unduly massive (hundreds of thousands of tons), hence prohibitively expensive to transport from Earth. The solution is to include only a few representative components of the railgun system with the initial seed that is landed on the Moon. The initial seed factory then makes negative castings of these components in situ, producing templates which can be used to cast thousands of copies of the heavy components in metal, on the Moon.

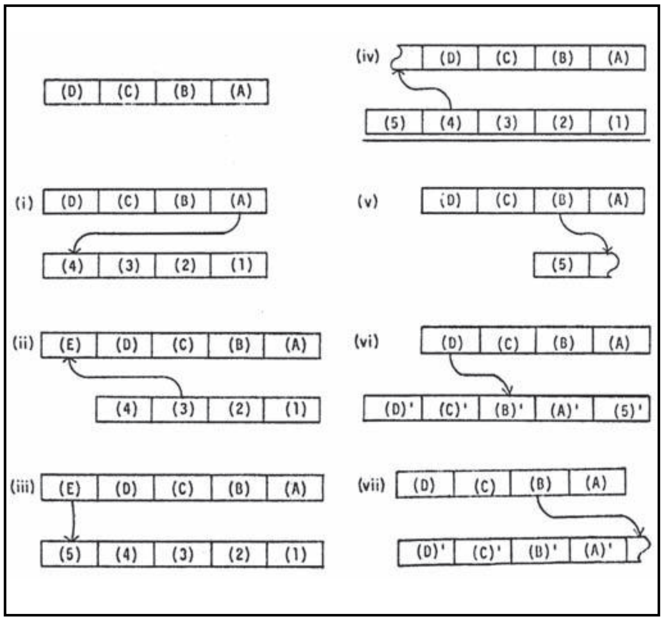


Figure 2.9. Laing's self-reproduction by self-inspection. (courtesy of Laing[561])

Suthakorn and Chirikjian[2341] have also demonstrated a non-von-Neumann architecture for the replication of a LEGO®-based transistor circuit by active self-inspection. "There are no instructions stored about how to construct the circuit, but information observed about the spatial organization of the original circuit is fed into the circuit itself to provide assembly commands. The circuit then drives a larger electromechanical (robotic) system in which it is embedded to cause the production of a replica of the original circuit. In the current context, the electromechanical hardware is viewed as a tool which is manipulated by the control circuit for its own reproduction (much in the same way that deer living in a forest can reproduce without an associated reproduction of the forest itself)."

2.3.6 Nonautonomous Machine Replication

Machines can also replicate their physical structure without containing their own description if the instructions are fed to them, one by one, from some outside source without the machine having any onboard capacity for computation or even data storage. One simple example of this strategy is the broadcast architecture.[208-210] In this approach (see also Section 4.11.3.3), information is broadcast by any of various means to the replicating component. The physical replicator becomes, in essence, a remote-controlled or "teleoperated" manipulator receiving external instructions that guide it, step by step, in assembling a second remote-controlled manipulator. After some number of repeat cycles, the result is a large number of identical remote-controlled manipulators which can then be employed to manufacture large numbers of useful product objects by altering the stream of instructions sent to the population of replicated manipulator devices.

This architecture was partially anticipated by Laing,[556] who discussed the implementation of a free-floating automaton system with activation signals transmitted diffusively through fluid in a biological context, and by Holland,[575] who offered a carefully worked out formalism for such "broadcast" communication automaton systems. Laing[556] notes that as a general design principle, "we can dispense with some of the structural complexity of our artificial organisms provided we compensate by increasing the number or the functional complexity of the signal types....By augmentation of signal complexity, we [can] overcome degradation of physical structure and obtain the desired result." Thus Laing disposed of the requirement for logical universality to achieve self-replication, much as Langton had earlier disposed of the requirement for constructional universality (Section 2.2.1).

Other examples of nonautonomous kinematic machine replication are the "exponential assembly" scheme proposed by Skidmore et al[576] (Section 4.17) and the electrophoretic system for stepwise exponential growth of DNA-based chemical replicators proposed by von Kiedrowski's group.[1362,1428,1429]

2.3.7 Embodied Evolution: Algorithmic Replication

A more limited form of self-replication, originally addressed by Husbands and Harvey[577] and others[578-593] as "evolutionary robotics," has recently been investigated experimentally as "embodied evolution" by Watson et al.[594] In these experiments, an evolutionary algorithm is distributed amongst and embodied within a population of eight physical mobile robots that "reproduce" with one another and "evolve" together, in a specialized task environment (e.g., a demonstration of phototaxis). Although the robot population is fixed in size and membership, operating algorithms are transferred among the various robot members by "broadcasting a gene," analogous to the sharing of genetic information by promiscuous microorganisms. There is no "reproduction mode" as such because reproduction is concurrent with task behavior.[582] According to the researchers:[594] "Assuming that we cannot really create new robots spontaneously, the offspring must be implemented using (other) robots of the same population. And, if the robots do not have structurally reconfigurable bodies, reproduction must simply mean the exchange of control program code." This approach "enables the study of the effects of integrating reproduction with other autonomous behaviors into real robots in a manner that has previously only been possible in simulated ALife experiments," although the authors caution that "reproduction may interfere with task behavior."

The authors[594] point out that the artificial life literature provides several examples[442,595-597] of simulated systems where agent behavior and reproductive activity are integrated, but heretofore experiments using physical robots have not been able to integrate reproduction with other autonomous behaviors. Also noteworthy are the attempts by Lund et al[600] to evolve (in simulation) both a robot control program and some parameters of the robot's physical body including number of sensors, sensor positions, body size, turret radius, and so forth. The evolution can explore only those parameters foreseen by the designer and cannot produce "creative" new designs, consistent with our desire for our machines to exhibit "safe" replication (Section 5.11).

CHAPTER 3

Macroscale Kinematic Machine Replicators

Specific proposals and realizations of von Neumann’s kinematic replicators and related physical implementations of macroscale machine replicators or self-replicating factory systems are of the greatest interest in the context of this book. Penrose,[683] quoting Kemeny,[243] complained that the body of the von Neumann kinematic machine “would be a box containing a minimum of 32,000 constituent parts (likely to include rolls of tape, pencils, erasers, vacuum tubes, dials, photoelectric cells, motors, batteries, and other devices) and the ‘tail’ would comprise 150,000 [bits] of information.” Macroscale kinematic replicators will require a great deal of effort to design and to build, which may explain why so few working devices have been constructed to date,* despite popular interest.[652,653,2907] However, small devices that can assemble themselves from a few simpler parts have proven remarkably easy to build. Conventional factory automation technology continues to evolve toward increasingly flexible manufacturing systems that are collectively capable of self-replication. A fair number of specific macroscale self-replicating machine systems have been proposed in some detail, and a handful have been physically constructed and even patented.[650,651] In this Chapter we describe and review these pioneering theoretical proposals and experimental efforts.

3.1 Moore Artificial Living Plants (1956)

Von Neumann’s deductions on the logic of replication in the late 1940s and early 1950s were highly abstract and known only to a few specialists who had heard his lectures,** until Kemeny’s 1955 article[243] in *Scientific American* brought these concepts to a wider audience. Just one year later, in 1956, mathematician and scientist Edward F. Moore offered the first known suggestion for a real-world application of kinematic self-replicating machines, representing the vanguard in a long line of commentators who would later expound upon the powerful economic potential of exponential growth among populations of such devices.

“It is unlikely that the [kinematic] machine von Neumann described will ever actually be built, because it would have no useful purpose except as a demonstration,” noted Moore in his 1956 *Scientific American* article.[677] But then he continued:

“I would like to propose another type of self-reproducing machine, more complicated and more expensive than Von Neumann’s which could be of considerable economic value. It would make copies of itself not from artificial parts in a stock room but from materials in nature. I call it an artificial living plant (Figure 3.1). Like a botanical plant, the machine would have the ability to extract its own raw materials from the air, water and soil. It would obtain energy from sunlight — probably by a solar battery or a steam engine. It would use this energy to refine and purify the

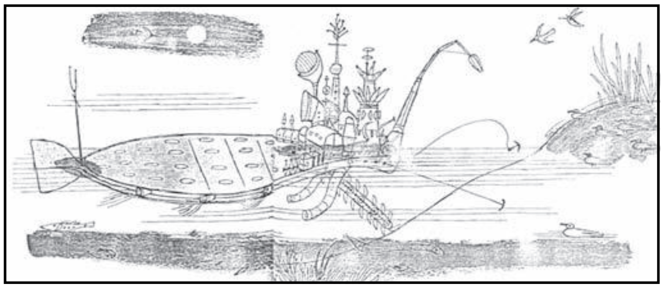


Figure 3.1. Artist’s conception of Moore’s artificial living plant, from Moore.[677] This artificial living plant is jet-propelled, on the model of the squid. When securely moored, it will begin the process of replication.

---

* *At the Second International Conference on Evolvable Systems in 1998 (ICES98), the Program Chair, Moshe Sipper, arranged for an official “Self-Replication Contest” to be held during the conference.*[654] *The object of the contest was to “demonstrate a self-replicating machine implemented in some physical medium, e.g., mechanical, chemical, electronic, etc.” The rules further stated that: “The machine must be demonstrated AT THE CONFERENCE site. Paper submissions will not be considered. The most original design will be awarded a prize of $1000 (one thousand dollars). The judgment shall be made by a special contest committee. The committee’s decision is final and incontestable.” Despite the financial enticement, no entries were received.*

** *A short story by science fiction writer Philip K. Dick, entitled “Autofac,” describes a nationwide system of automated factories that produce food, consumer goods, and “miniature replicas” of more factories, perhaps one of the first descriptions of autonomous machine self-replication to appear in this genre,*[668] *though a few related stories describing replicated robots appeared in the 1920s*[657-659] *and 1930s.*[660] *Dick’s story ends with the factory, when it is almost destroyed, shooting out a torrent of metal seeds that germinate into miniature factories — which from today’s more informed perspective we might interpret as self-replicating nanorobots.*[303] *“Autofac” was published in November 1955, but it has been claimed*[668] *that Dick completed the story no later than 11 October 1954, which would appear to predate Moore’s article and possibly Kemeny’s article as well, though not, of course, von Neumann’s original 1948 lecture.*[317] *(Dick wrote about von Neumann’s game theory,*[655] *so he’d probably read von Neumann’s self-replication work as well.) Earlier stories by Dick in 1952*[665] *and 1953*[666] *had described self-repairing or self-replicating, evolving war machines that inherit an entire planet. (*Vulcan’s Hammer *(1960),*[656] *a later novel by Dick, continued his theme of an autonomous computer able to expand and rebuild itself.) “Epilogue,” a science fiction story published by Poul Anderson in 1962,*[669] *describes self-replicating factory barges using minerals extracted from ocean water as raw materials and is more clearly derived from Moore’s speculations. Contemporary science fiction writers frequently returned to the theme of self-replicating robots in the 1950s,*[661-663] *1960s,*[671-674] *1970s,*[2936] *1980s,*[693,694] *1990s,*[675,676] *and 2000s.*[2898]

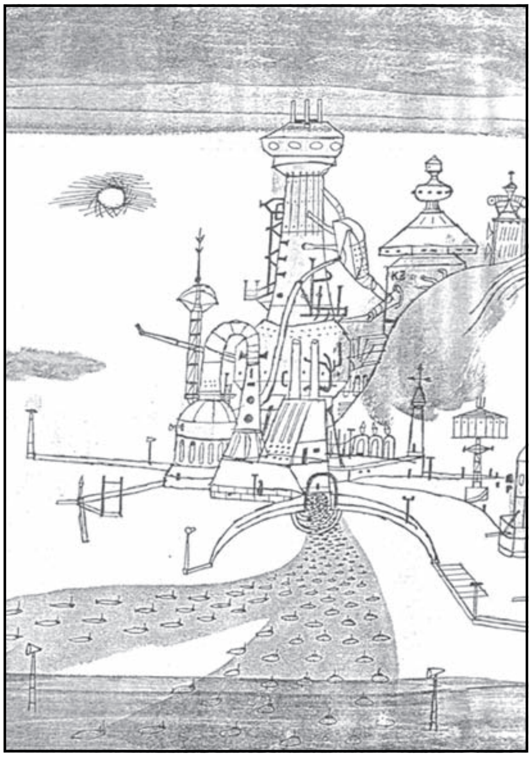


Figure 3.2. Harvesting Moore's artificial living plants, from Moore.[677] Like lemmings, a school of artificial living plants swims into the maw of the harvesting factory.

materials and to manufacture them into parts. Then, like Von Neumann's self-reproducing machine, it would assemble these parts to make a duplicate of itself.

"For the first model of such a machine, a good location would be the seashore, where it could draw on a large variety of available materials. The air would provide nitrogen, oxygen and argon; the sea water would provide hydrogen, chlorine, sodium, magnesium, sulfur…; the beach would provide silicon and possibly aluminum and iron….From these elements the machine would make wires, solenoids, gears, screws, relays, pipes, tanks and other parts, and then assemble them into a machine like itself, which in turn could make more copies….The next step would be to tackle the harder problems of designing artificial living plants for the ocean surface, for desert regions or for any other locality having much sunlight but not now under cultivation. It is easy to see that a plant of this kind could have considerable economic value. It could be harvested for a material it extracted or synthesized, just as cotton, mahogany and sugar cane are now harvested from plants in nature. Thus an artificial plant which used magnesium as its chief structural material could be harvested for its magnesium.

"If the object is to manufacture a specific product, would it not be much simpler to design an automatic factory to make it, rather than to go to all the trouble of creating an artificial living plant? It would indeed be simpler, but obviously the returns would not be as great. Where a factory turns out products at a constant rate, the production of the artificial living plant would grow exponentially. If its net reproduction time were one year, after 30 years there would be more than a billion of these plants! Needless to say, they could not be allowed to reproduce indefinitely, for they would soon fill up the oceans and the continents….It might be worth while to build into these plants a tendency to migrate, like lemmings, to preassigned locations where they could be harvested conveniently (Figure 3.2)."

Commenting on Moore's plan years later, in 1972, Freeman Dyson[2934] observed that: "It may well happen that on Earth, for aesthetic or ecological reasons, the use of self-reproducing machines will be strictly limited and the methods of biological engineering will be used instead wherever this alternative is feasible. For example, self-reproducing machines could proliferate in the oceans and collect minerals for man's use, but we might prefer to have the same job done more quietly by corals and oysters. If economic needs were no longer paramount, we could afford a certain loss of efficiency for the sake of a harmonious environment. Self-reproducing machines may therefore play on Earth a subdued and self-effacing role."

3.2 Browning Unnatural Living State (1956, 1978)

In 1956, the late Dr. Iben Browning (d. 1990) was selected to head a newly-formed independent Research Division at Bell Aircraft Corporation of Buffalo, New York. The first technical report[678] produced by the new Division, authored by Browning and published in December 1956, purported to present a "periodic table of the physical universe" — that is, a comprehensive classification scheme for research that encompassed studies of all material objects at all size scales. The table listed four different states of matter and the disciplines associated with them including: (1) the natural non-living state, (2) the natural living state, (3) the unnatural non-living state, and (4) the unnatural living state. Unfortunately, the fourth category was censored out of the report by Browning's superiors at Bell Aircraft and did not see print until 1978, when the full report (with the deleted text restored) was reprinted by Winkless and Browning in their book *Robots On Your Doorstep.*[679]

According to Winkless,[679] writing about these events two decades later in 1978, the fourth category provided a discussion of "...robots that could reproduce. It seems not wholly implausible these days that machines might be constructed that could build other machines just like themselves. Given what we know about computers, we can even imagine that these machines might have artificially constructed and programmed reflexes and responses that would help them survive, avoid hazards in the real world, and seek the materials needed for construction of more of their kind. In 1956 this was more than Bell Aircraft Corporation could bear. The subject was just too far out, damaging to the reputation and practical effectiveness of the company. The robots were eliminated from the proceedings...." Dr. Browning left the company soon afterwards, perhaps discouraged when an assistant vice-president diverted a significant portion of the new Research Division budget to hire a psychic medium advisor for Bell Aircraft Corporation.

In his original 1956 report,[678] Browning mentions only three prior discussions — by Karel Capek (Chapter 1), von Neumann (Section 2.1) and Moore (Section 3.1) — asserting that "the abilities of Man have enabled him to design devices that will reproduce. It is not unreasonable to expect that machines will reproduce themselves, in the light of current knowledge of automated machines of all sorts including computer controls. Huge memory banks can be made with trillions of bits of memory now. With optical techniques, it is clear that it is only a matter of time until memory systems can be made that are millions of times larger." Browning then named a few of the future fields of study that might deal with self-replicating robots, including "robot culturing" and "machine (or robot) husbandry" to produce "simple self-reproducing robots"; "psycho-robotics" for the study of "hetero-functional robots" and various "robotypes"; and "socio-robotics" which would study communities of various robotypes using "community robodynamics", or entire robotic populations using "gross robodynamics".

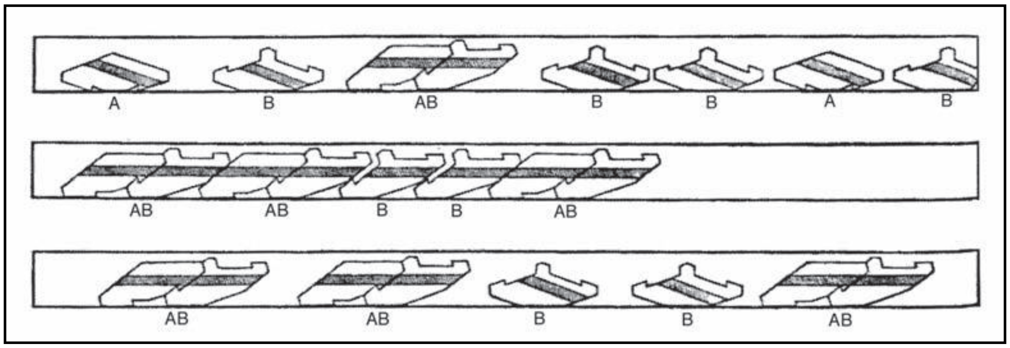


Figure 3.3. A 1-D self-replicating machine made of parts of two kinds, from Penrose.[681]

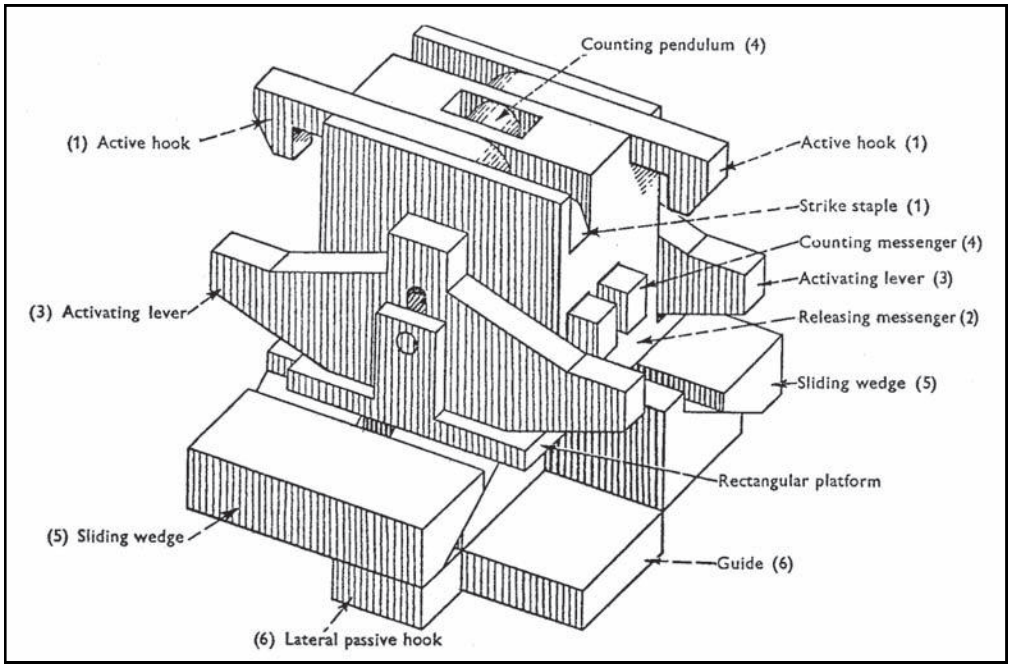


Figure 3.4. A double-hook "food" unit for Penrose block replicator, from Penrose.[681]

3.3 Penrose Block Replicators (1957-1962)

The first known physical implementation of simple machine replication was reported by the British geneticist Lionel S. Penrose at University College, London, and his son, the physicist Roger Penrose at Bedford College, London, in 1957.[680] They started by defining some ground rules[681] for such efforts: "A structure may be said to be [self-replicating] if it causes the formation of two or more new structures similar to itself in every detail of shape and also the same size, after having been placed in a suitable environment. One of the new structures may be identical with the original one; alternatively, the original structure may be destroyed in the process of forming two new replicas. Certain conditions are added which exclude all well-known types of physical or chemical chain reactions. First, the replicating structure must be built by assembling simpler units present in the environment. Secondly, more than one design can be built from the same set of units though the only replicating structure that can be automatically assembled will be one exactly copying a previously existing structure. The pre-existing structure is known as a seed."

The first[680] in the Penrose family of replicators was a set of "A" and "B" type tilt-blocks, cut from plywood or vulcanite, and placed on a track where they could slide freely but not pass each other. When single parts are placed on the track and subjected to horizontal agitation, they do not join together. However, when an interlocked, two-block "AB" or "BA" unit is placed in the box and shaken, a simple form of 1-dimensional replication takes place (Figure 3.3). Collisions between the two-block unit and other lone parts in the box cause new two-block units to form, each identical to the original, demonstrating self-replication as a simple form of mechanical autocatalysis.

L. Penrose[681-685] went on to devise an ingenious interlocking column design which allowed the replication of a multipart machine which is free to move about in a 2-dimensional agitation environment strewn with a random assortment of premanufactured constitutive columns. The replicating machine consists of two interlocking columns of five blocks each, with clever arrangements of springs, levers, hooks, dovetails, and ratchets on each of the parts. Each column includes five blocks stacked vertically: two double-hook blocks which act as neutral "food" for a fully automatic replicating structure of any required length (Figure 3.4), one activating cam lever block that transmits activation but does not link (Figure 3.5), one blocking device that prevents more than four units from coming close together (Figure 3.6), and a footing block consisting of interdigitating bases upon which superstructures capable of activation, hooking and release could be mounted, permitting machines to operate in 2 dimensions and to orient themselves to one another for the purposes of self-replication (Figure 3.7).

The complete 2-D self-replicating machine (Figure 3.8) is the double-column seed unit at center (a) — linked by double hooks, incorporating the tilted cam-lever activating principle, and protected by the blocking device in its base (interdigitating footing blocks not shown). Explains Penrose:[683] "When the neutral unit at left joins the seed (b), it disengages one of the hooks holding the seed together and sets the blocking mechanism so that only one more neutral unit

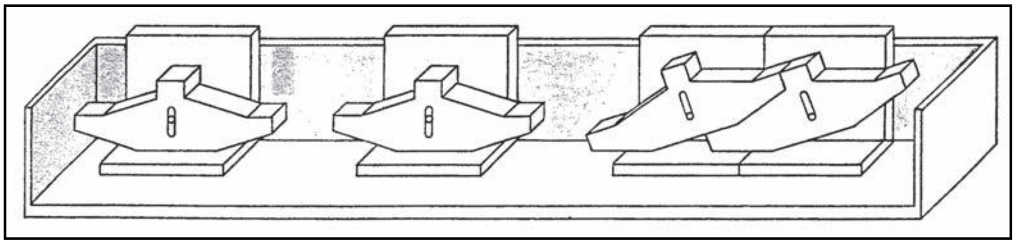


Figure 3.5. Activating cam levers for Penrose block replicator, from Penrose.[683]

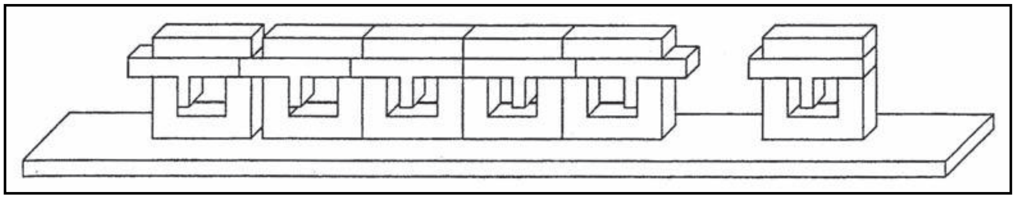


Figure 3.6. Four-unit blocking device for Penrose block replicator, from Penrose.[683]

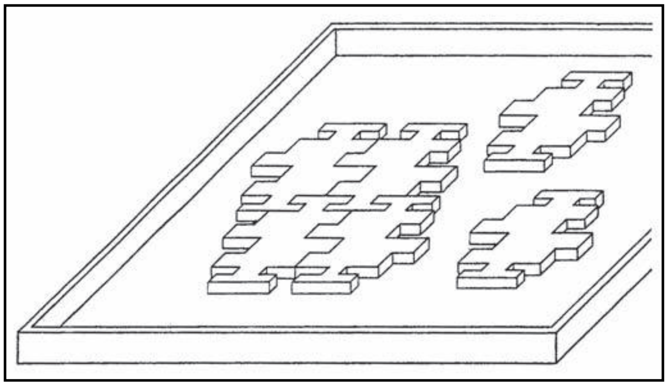


Figure 3.7. Interdigitating bases for Penrose block replicator, from Penrose.[683]

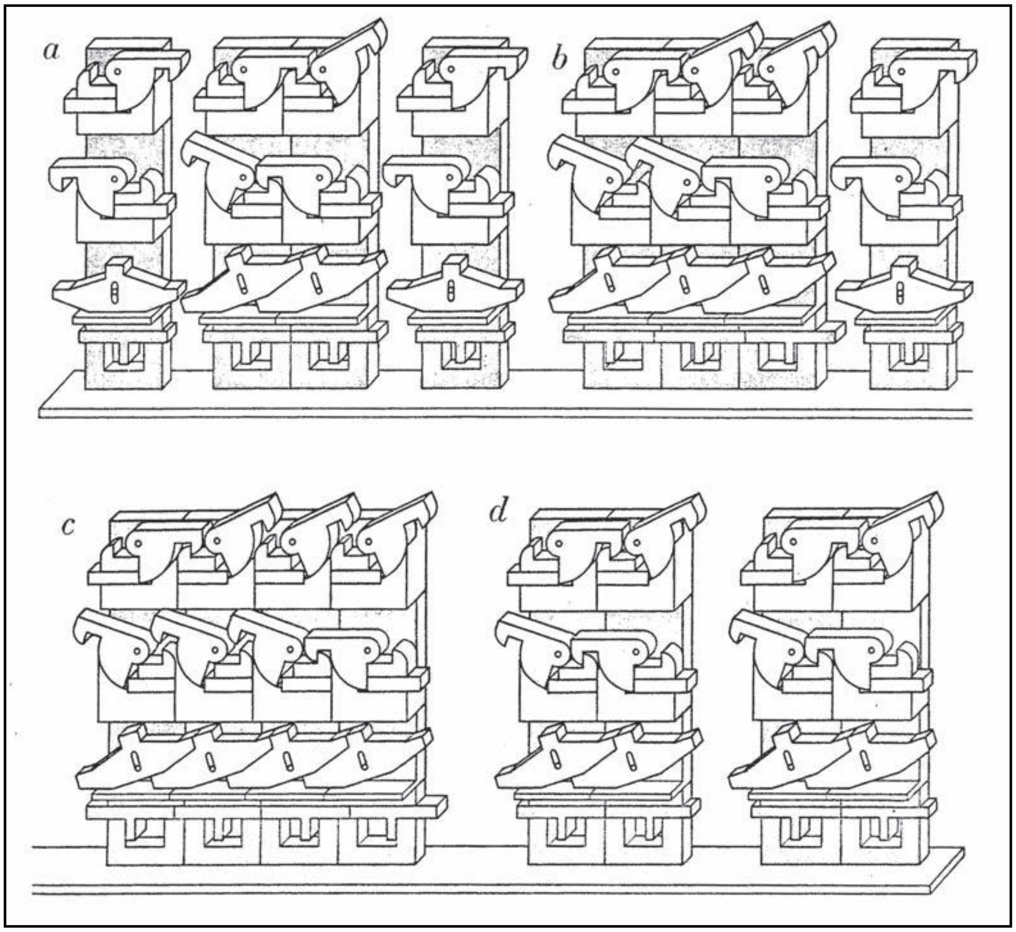


Figure 3.8. One replication cycle of the Penrose block replicator, from Penrose.[683]

can be added. When the fourth unit joins the triple group (c), it disengages the second hook in the original seed, causing it to come apart in the middle and form two replicas of itself (d)."

An 11-minute movie was made of the replicating blocks in action by H.A. Cresswell in 1958.[686] Interestingly, in the finest scientific tradition, the simplest of Penrose's machine replicator designs was independently "replicated" (confirmed) in 1962 by another well-known scientist, Edward F. Moore, who wrote:[353] "After constructing an exact copy of Penrose's basic model, I have found that it not only operates mechanically with reasonable satisfaction, but is very useful in suggesting to audiences some of the problems and possibilities of self-reproducing machines. If the reader attempts the problem of how to design the shapes of the units A and B so as to have the specified properties, the difficulties he will encounter in his attempt will cause him to more readily appreciate the ingenuity of Penrose's very simple solution to this problem."

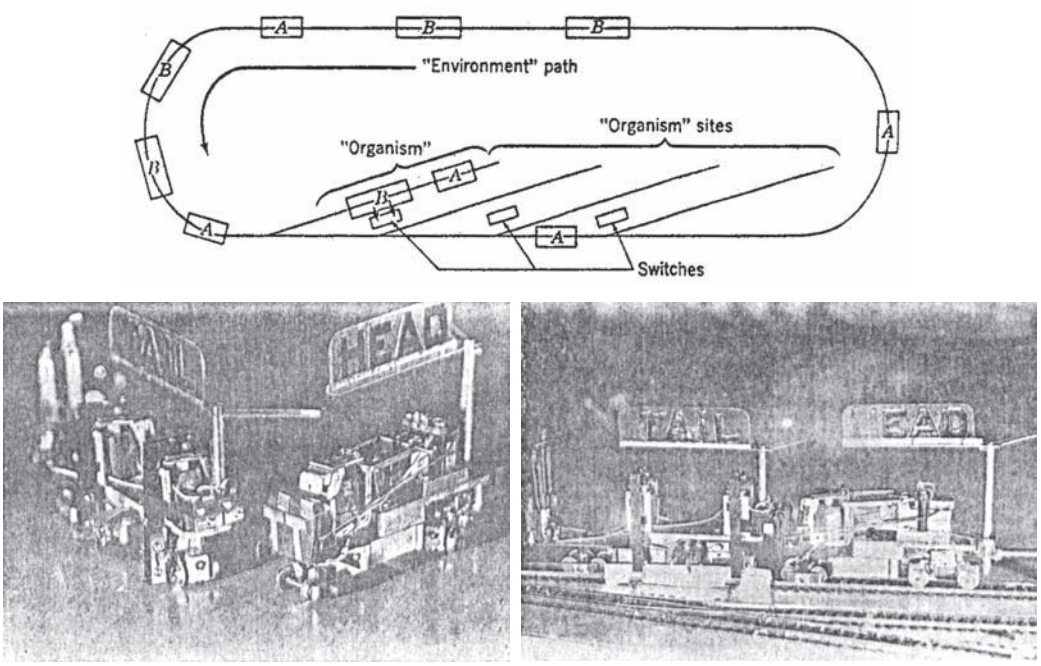
New generations of similar conformation-switched blocks are currently being pursued by Griffith (Section 3.28) and by Saitou[1546] in the context of the self-assembly of microscale mechanical parts (Section 4.1.5). Prions (Section 4.3.1) also represent a crude biological analog of the Penrose block system.

3.4 Jacobson Locomotive Toy Train Replicator (1958)

In 1958, Homer Jacobson,[687] a physicist at Brooklyn College in New York, was considering how one might build a self-replicating machine using electromechanical components. He started by noting that the essentials in a kinematic self-replicating system are: (1) an environment in which random elements, or parts, circulate freely; (2) an adequate supply of prefabricated parts; (3) a usable source of energy for assembly of these parts; and (4) a pre-assembled seed replicator, composed of the available parts, capable of taking those parts from the environment and synthesizing them into a functional copy of its own assembly, using the available energy to do so. The first design that occurred to Jacobson was "a simple mechanical self-assembler, consisting of motor, plan, and sensor. Under control of the plan, the motor could move the sensor about a junkyard-like environment of parts, pick up the proper part, move it to some nearby assembly area, and perform any necessary assembly operations. The chief difficulty with designing such a model is in designing a motor which operates on parts at a distance, picks up a copy of itself, and drops it into an accurately positioned spot at some like distance. This difficulty of designing a motor to move all the parts could be eliminated by allowing the parts to move under their own power, i.e., be locomotive."

Working from this insight, Jacobson built a self-replicating device using modified parts from an HO train set (photographs of the actual working models have been published; Figure 3.9). In Jacobson's "Reproductive Sequence Device One" or RSD1, there are two kinds of programmed, self-propelled toy train engines, called heads and tails, that circulate individually in random sequence around a loop of track with several sidings (Figure 3.9). With the sidings empty, nothing happens. But if an ordered pair of engines, a head (A) and tail (B), comprising the replicator, is once assembled on a siding, then this replicator can cause more copies of itself to be assembled on adjacent sidings. This is simply accomplished as follows. First, the head car in the pair waits for a free head car to come by and, upon detecting it, orders the tail car to open a switch that shunts it onto the adjacent open siding. In similar manner, the next free tail car to come by is shunted onto that same siding to make a new head-tail pair. Once this happens the first toy engine couple turns itself off and the second pair becomes the active replicator. Replication continues to propagate in linear fashion "until the environment runs out of parts, or there are no more sidings available, or a mistake is made somewhere in the operation of a cycle." Note that a great deal of functionality essential for replication resides in the environment, including the spacer system, siding end stops, and motor cutoffs.

A more sophisticated device, the RSD4, would allow both the duplication of a replicator according to a set of plans in the parent, but also would allow for the duplication of the plans during replication, in keeping with the von Neumann kinematic motif. In the RSD4 (Figure 3.10), which was designed but apparently never built, the replicator now consists of three toy engines — a head (A), body (B), and tail (C). Heads and tails circulate freely as before, but there



B and A cars, with bumper contact detail.

Single assembled "organism."

Figure 3.9. Physical replication using Jacobson locomotive toy train cars with fixed plan, from Jacobson.[687]

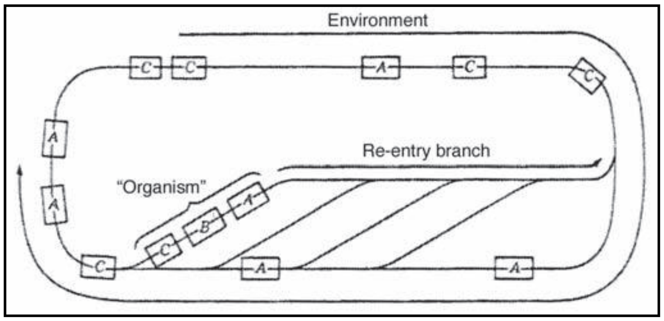


Figure 3.10. Physical replication using Jacobson locomotive toy train cars with replicated plan, from Jacobson.[687]

is only one body, containing the plan, in the replicator. Tail and body toy engines are identical, except the former contains an unpunched card, which, upon being punched with the plan, is converted to a body car that is released back into the environment via the re-entry branch of track.

3.5 Morowitz Floating Electromechanical Replicator (1959)

In 1959, Harold Morowitz[688] designed (but did not actually build) a very simple replicator consisting of two components (Figure 3.11) having the density of water. The device resides in a sea of floating parts (perhaps in a large tub of water) agitated constantly by a stirrer. The first component (A) is a complex unit consisting of an electromagnet with a soft iron core, one sliding rod, two batteries, two microswitches, two metal plates forming an open capacitor, and some wire. The second component (B) is an electret that docks into a port on the first component; with the electret in place, the electromagnet is turned on. An AB replicator selects an A part and a B part from the environment, assembles them into an AB daughter replicator, then releases the daughter AB unit back into the environment, completing the act of replication.

A single 5-step replicative cycle (see Figure 3.12) proceeds as follows:

> **Step 1**. The parent replicator's electromagnet is on, attracting the soft iron bar of an inert "A" part.
>
> **Step 2**. The joining of an "A" to the parent pushes in the sliding rod, closing one microswitch and activating the capacitor.
>
> **Step 3**. An electret "B" part that collides with the port is pulled into position by the capacitor, completing the assembly.
>
> **Step 4**. Insertion of the electret closes the second microswitch, activating the daughter's electromagnet.
>
> **Step 5**. The two electromagnets repel, separating daughter from parent, and the replicative cycle is complete.

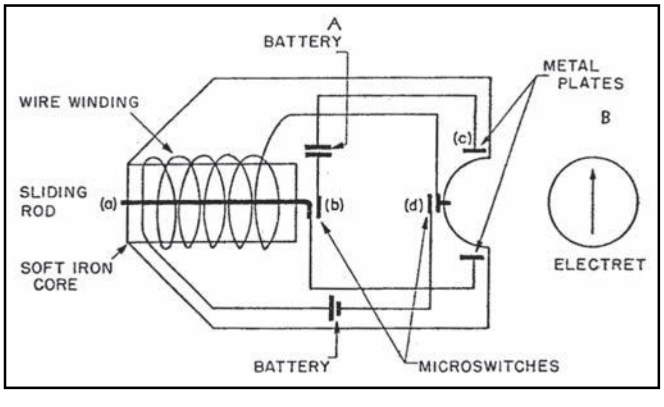


Figure 3.11. Design of the Morowitz floating electromechanical replicator, from Morowitz.[688]

3.6 Dyson Terraforming Replicators (1970, 1979)

In his Vanuxem Lecture in 1970, delivered just four years after Burks' 1966 publication of the edited works of von Neumann on self-reproducing automata[3] (which brought von Neumann's concepts to the attention of an even larger community of scientists and engineers), physicist Freeman Dyson suggested three large-scale applications of kinematic machine replicators as "thought experiments" for the 21st century:[1034]

Enceladus replicator (1970). "We have the planet Mars, a large piece of real estate, completely lacking in economic value because it lacks two essential things, water and warmth. Circling around the planet Saturn is a satellite called Enceladus. Enceladus has a mass equal to five percent of the earth's oceans, and a density rather smaller than the density of ice. It is allowable for the purposes of a thought experiment to assume that it is composed of dirty ice and snow, with dirt of a suitable chemical composition to serve as construction material for self-reproducing automata.

"The thought experiment begins with an inconspicuous rocket, carrying a small but highly sophisticated payload, launched from the Earth and quietly proceeding on its way to Enceladus. The payload contains an automaton capable of reproducing itself out of the materials available on Enceladus, using as energy source the feeble light of the far-distant sun. The automaton is programmed to produce progeny that are miniature solar sailboats, each carrying a wide, thin sail with which it can navigate in space, using the pressure of sunlight. The sailboats are launched into space from the surface of Enceladus by a simple machine resembling a catapult. Gravity on Enceladus is weak enough so that only a gentle push is needed for

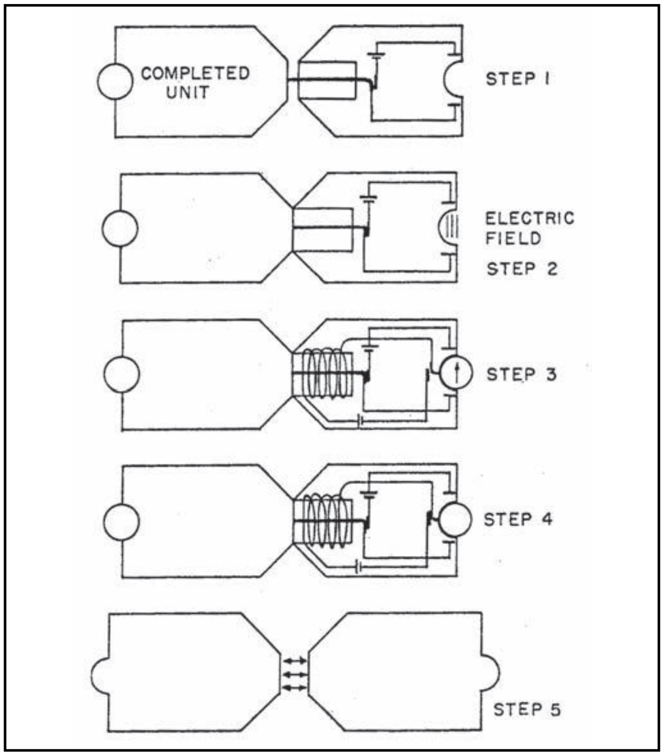


Figure 3.12. Replication cycle of the floating electromechanical replicator, from Morowitz.[688]

the launching. Each sailboat carries into space a small block of ice from Enceladus. The sole purpose of the sailboats is to deliver their cargo of ice safely to Mars. They have a long way to go. First they must use their sails and the weak pressure of sunlight to fight their way uphill against the gravity of Saturn. Once they are free of Saturn, the rest of their way is downhill, sliding down the slope of the Sun's gravity to their rendezvous with Mars.

"A few years later, the night-time sky of Mars begins to glow bright with an incessant sparkle of small meteors. The infall continues day and night, only more visibly at night. Day and night the sky is warm. Soft warm breezes blow over the land, and slowly warmth penetrates into the frozen ground. A few years later, it rains on Mars for the first time in a billion years. It does not take long for the oceans to begin to grow. There is enough ice on Enceladus to keep the Martian climate warm for ten thousand years and to make the Martian deserts bloom."

Desert replicator (1970). "One of the byproducts of the Enceladus project is a small self-reproducing automaton well-adapted to function in terrestrial deserts. It builds itself mainly out of silicon and aluminum which it can extract from ordinary rocks wherever it happens to be. It can extract from the driest desert air sufficient moisture for its internal needs. Its source of energy is sunlight. Its output is electricity, which it produces at moderate efficiency, together with the transmission lines to deliver the electricity wherever you happen to need it....The progeny of one machine can easily produce a hundred times the present total power output of the United States, but nobody can claim that it enhances the beauty of the desert landscape....The rock eating automaton generates no waste heat at all. It merely uses the energy that would otherwise heat the desert air and converts some of it into useful form. It also creates no smog and no radioactivity. Legislation is finally passed authorizing the automaton to multiply, with the proviso that each machine shall retain a memory of the original landscape at its site, and if for any reason the site is abandoned the machine is programmed to restore it to its original appearance.

"If solar energy is so abundant and so free from problems of pollution, why are we not already using it on a large scale? The answer is simply that capital costs are too high. The self-reproducing automaton seems to be able to side-step the problem of capital. Once you have the prototype machine, the land, and the sunshine, the rest comes free. The rock-eater, if it can be made to work at all, overcomes the economic obstacles which hitherto blocked the large-scale use of solar energy."

Industrial development kit (1970). "After its success with the rock-eating automaton in the United States, [the company] places on the market an industrial development kit, designed for the needs of developing countries. For a small down payment, a country can buy an egg machine which will mature within a few years into a complete system of basic industries together with the associated transportation and communication networks. The thing is custom made to suit the specifications of the purchaser. The vendor's guarantee is conditional only on the purchaser's excluding human population from the construction area during the period of growth of the system. After the system is complete, the purchaser is free to interfere with its operation or to modify it as he sees fit." (Compare the "mini-plants" described in Section 3.7.)

"Another venture...is the urban renewal kit. When a city finds itself in bad shape aesthetically or economically, it needs only to assemble a group of architects and town planners to work out a design for its rebuilding. The urban renewal kit will then be programmed to do the job for a fixed fee."

Replicating water plants (1979). In 1979, Dyson[1042] added a fourth application of kinematic replicators — a modified version of Moore's artificial living plants (Section 3.1) wherein each seagoing device "carries a large tank which it gradually fills with fresh water separated by solar energy from the sea...it is also prepared to use rain water as a bonus when available. Any boat with a full cargo of fresh water is programmed to proceed to the nearest pumping station, where it is quickly pumped dry and sent on its way."

Freitas (1983),[1079] Morgan (1994),[689] Nussinov et al. (1994),[690] Coppinger (1996),[691] and Gillett (1996)[692] have subsequently discussed using machine self-replicating systems for terraforming other planets, and related concepts have appeared frequently in the science fiction literature.[693-696]

3.7 Self-Replicating Automated Industrial Factory (1973-present)

For nearly two centuries fiction has portrayed the increasingly automated mechanisms of evolving industrialism. For example, in 1897 Lathrop[697] imagined that in the 22nd century vast automated factories would be run by a single person at a keyboard. The following comments, attributed[698] to Konrad Zuse (1910-1995), builder of the world's first programmable digital computer in 1941 (Section 6.3.4), which were apparently communicated to the writer sometime in the early- or mid-1980s following the 1980 NASA lunar factory study (Section 3.13), express a similar anticipation:

> *Another idea of mine was "The Self-Reproducing System." I approached this concept differently to John von Neumann, who dealt with it using pure mathematics in the context of cellular computers. As an engineer I was more interested in setting up the conditions necessary for actual construction. In essence, the idea envisages a tool factory which is capable of reproducing its own essential component parts. This idea has met with complete opposition. People have been reluctant to consider such a radical solution for all sorts of reasons. Today traditional means of production are being automated step by step. We have yet to build the factory of the future. But one day these far-sighted developments will become reality, leading to a complete revolution in the production process throughout the economy.*

Over the last several decades there has been much progress in developing highly automated manufacturing systems wherein direct human interaction with the workflow is minimized, and in developing flexible manufacturing systems whose production line can be rapidly reconfigured for alternative products. The end result of this technical evolution could be an industrial factory capable of fabricating and assembling all of the parts of which it is comprised, resulting in a self-replicating factory system — even if none of the individual machines within that factory could directly replicate themselves.

In the early 1970s, Merchant[699] suggested that a fully automatic factory capable of producing and assembling machined parts could consist of modular manufacturing subsystems, each controlled by a hierarchy of computers interfaced with a larger central computer. The modular subsystems would perform seven specific manufacturing functions:

Product design by an advanced "expert system" software package or by humans remotely or interactively, using a computer design system that stores data on models, computes optimal designs for different options, displays results for approval, and allows efficient process iteration.

Production planning, an optimized plan for the manufacturing processes generated by a computer on the basis of product-design outputs, scheduling, and line-balance algorithms, and varying conditions of ore-feedstock deliveries, available robot resources, product mix and priorities. Planning includes routing, timing, work stations, and operating steps and conditions.

Parts forming at work stations, each controlled by a small computer able to load and unload workpieces, make parts and employ adaptive control (in-process operation sensing and corrective feedback), and incorporate diagnostic devices such as tool-wear and tool breakage sensors. (By 2004, machine parts could be designed, priced, ordered, machined and shipped online[752]).

Materials handling by different computer-controlled devices such as lifts, warehouse stacking cranes, carts, conveyors, and industrial robots with or without sensors that handle (store, retrieve, find, acquire, transport, load, unload) parts, tools, fixtures and other materials throughout the factory.

Assembly of parts and subassemblies at computer-controlled work stations, each of which may include a table, jigs, industrial robots with or without sensors, and other devices.

Inspection of parts, subassemblies and assemblies by computer-controlled sensor systems during and at the end of the manufacturing process.

Organization of production information, a large overseeing computer system that stores, processes, and interprets all manufacturing data including orders; inventories of materials, tools, parts, and products; manufacturing planning and monitoring; plant maintenance; and other factory activities.[700]

Historically, the Japanese have been the most aggressive in pursuing the "total automation" concept. During 1973-1976 their Ministry of International Trade and Industry (MITI) supported a study[701] entitled "Methodology for Unmanned Manufacturing" (MUM), which forecast some rather ambitious goals, including explicitly the capability "of expansion, self-diagnosis and self-reproduction." The MUM factory was to be operated by a 10-man crew, 24 hours per day, replacing a conventional factory of about 750 workers. The facility would be capable of turning out about 2000 different parts. The study led to a seven-year national R&D program at a funding level of 12 billion yen (about $57 million) to develop, establish, and promote technologies necessary for the design and operation of a "flexible manufacturing system complex".[702] One of the most significant characteristics of such massive automation is the possible regenerative or "bootstrapping" effect. Using robots to make robots should decrease costs dramatically, thus expanding the economically viable uses of robots. This, in turn, increases demand, leading to yet further automation, which leads to lower-cost robots, and so on. The end result is "superautomation".[703] A similar effect has already been seen in the computer industry wherein significant decreases in the price/performance ratio have continued unabated over four decades.

At a Tokyo conference on robotics in September 1980, Fujitsu Fanuc Ltd., a leading international manufacturer of N/C (numerical control) machining equipment, announced its plans[704,705] to open an historic robot-making factory near Lake Yamanaka in Yamanashi Prefecture in November. In this $38 million plant (which went into operation in January 1981[706,707]), industrial robots controlled by minicomputers manufactured other industrial robots virtually without human intervention. (The factory operated one or two shifts out of three without human attendance).[708] The plant, which was the first "unmanned" factory in the machinery industry, was originally expected to produce robots and other electronic equipment worth about $70 million in the first year of operation with only 100 supervisory personnel, expanding in five years (using some of its own manufactured robots) to a $300 million annual output with a workforce of only 200 people — less than a tenth of the number required in ordinary machine factories of equivalent output. A spokesman at the time said that Fanuc's fully automated system was suitable not only for mass production of a single product line, but also for limited production of divergent products.*

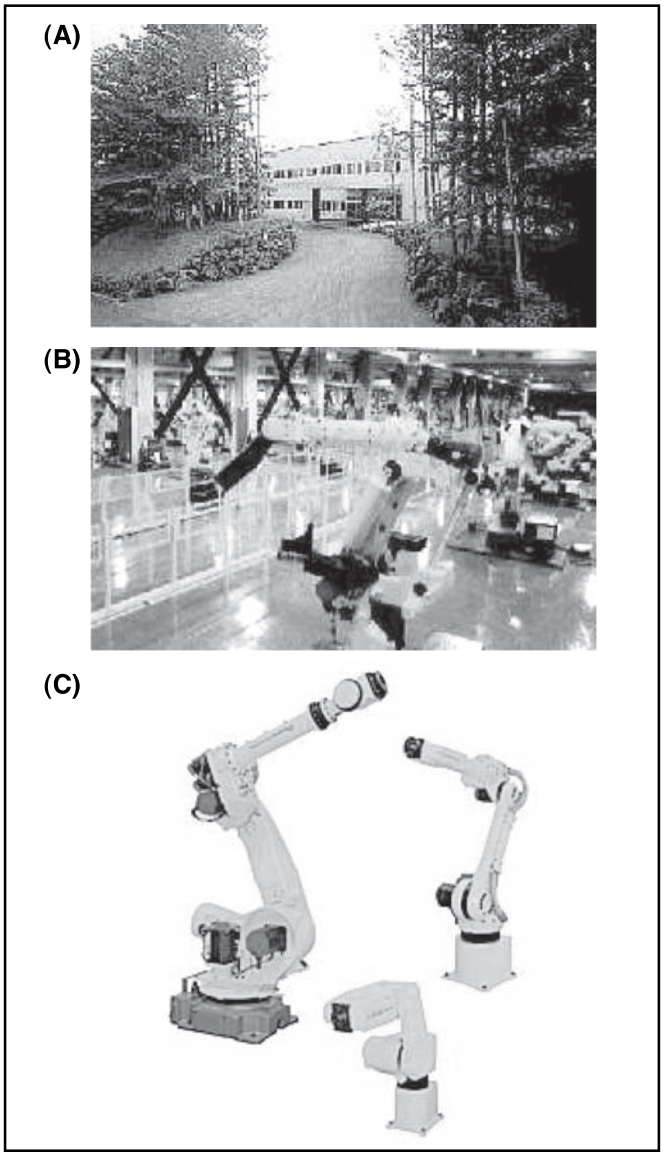


Figure 3.13. "Unmanned" robot factory[712] of Fujitsu Fanuc Ltd., reborn in April 1998: (A) new robot factory, (B) robot assembly line running test, and (C) the Fanuc Robot R-2000iA assembly robot.[716] (courtesy of Fujitsu Fanuc[712,716])

Unfortunately, notes Toth-Fejel,[711] this first attempt at an "unmanned" robot factory by Fanuc was economically unsuccessful and was eventually shut down, but later was reborn[712] in April 1998. In the new plant (Figure 3.13), a single Fanuc two-armed robot assembles smaller robots using a three-dimensional vision sensor and six force sensors that correct random positional errors. A different part of the factory (Figure 3.14) uses a distributive warehouse system for automatically assembling the larger robots.[713] Hence the robots in this factory are, effectively, self-replicating robots — the robots** can assemble selfsame robots, given parts. Other robotic

---

** At Nissan's carmaking plant in Japan in 1980,[709] "96% of the body assembly work done at our Zama plant is performed by automated machines: highly sophisticated, precision equipment that is controlled by computer and makes no mistakes." By 1980, the methods envisioned for MUM were being pursued vigorously by three Japanese government research institutes and twenty private companies, and were being managed by the Agency of Industrial Science and Technology of MITI.[710]*

*** According to the Fanuc "Robot Products" webpage:[716] "The FANUC Robot R-2000**iA** is a multi-purpose, intelligent robot integrating mechanical, electronic and artificial intelligence technologies. The Intelligent robots rely on vision sensors to locate and grasp parts of all sizes. Relying on force sensors, they can detect requisite force and perform assembly work. In these ways, work traditionally dependent on human senses and expertise is robotized, and system costs are reduced by eliminating peripheral equipment."*

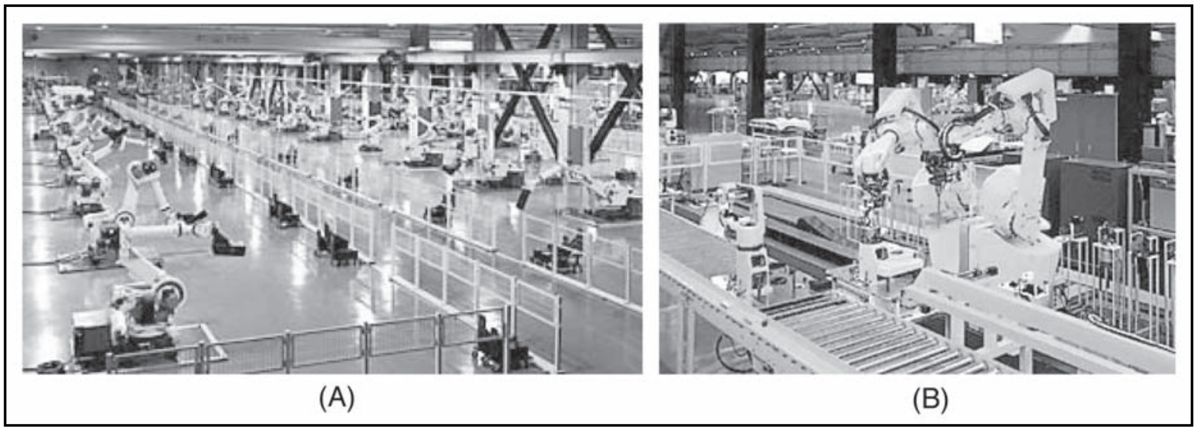


Figure 3.14. Fanuc Factory Group: Robot Factory. A two-armed intelligent robot equipped with vision and force sensors assembles mini-robots in place of human workers. Each assembled robot goes through a 100-hour running test and rigorous inspection before shipment; the factory has a capacity to produce 1,500 robots a month. (A) running test; (B) automatic assembly system with the two-armed intelligent robot.[717] (courtesy of Fujitsu Fanuc[717])

manufacturers, such as Yasukawa Electric, also use robots to make robot parts,[714] while Yamazaki Mazak has several FMSs (Flexible Manufacturing Systems) that machine the components for the CNCs (Computerized Numerical Controlled machines) that make up their FMSs.[715] Another area of automated assembly technology that applies to self-replication is high-flexibility assembly line technology, especially the type that can cope with the mixed-flow production of multiple output parts.

For more than two decades since the first Fanuc plant began making its own robots, futurists have been predicting the emergence of fully automated, "unmanned," or "lights-out factories," and these are slowly becoming more common,[718] particularly in continuous flow processes and other specialized areas. For example:

- IBM has a keyboard assembly factory in Texas that is totally lights-out.[719] A few engineers and technicians are on-site to support the machines, but human hands never touch the products during the manufacturing process. People drive trucks to the factory doors to deliver raw materials and to pick up finished products. The factory operates 24/7 with down time used for scheduled maintenance or repair. Since factory computers themselves have keyboards, the system arguably may be said to be partially self-replicating.
- At the Unifi Inc. textile manufacturing plant in Yadkinville, North Carolina, "everything is run by computers and there's nobody on the production floor".[720]
- When NeXT computers were still being produced in the early 1990s, the factory that assembled the computers used robotic assemblers which were themselves controlled by computers of a similar type.[721] This led to the observation that microcomputers were controlling robots that were making more microcomputers,[722] implying that the microcomputers were at least partially self-replicating.
- Fanuc Robotics claims a throughput of 320 robot-related parts per hour with a fully automated (unmanned) robot/lathe system.[723] They are developing[724] "a humanoid robot...capable of using its both arms to assemble and disassemble model robots." In June 2002 Fanuc announced[725] a new "robot cell" enabling 72-hour unmanned machining operations. In March 2003, they launched a new robot system[726] "capable of 24 hours continuous machining per day for 7 days." Interestingly, upon completion of new robotic factories in Japan, a priest usually conducts "a Shinto ritual to purify the newly added factory."[727]
- Haas Automation, Inc., of Oxnard, California, is the largest unit-volume producer of CNC machine tools in the United States, producing over 600 CNC machines for the first time in October 2000.[728] Their machine shop runs two shifts — the second is essentially "lights out" because of extensive automation — while machine assembly only runs one shift. Shipping generally takes place in the evening to avoid conflicts with assembly operations.[729]
- A private machine tool company in Leicester, U.K., performs production machining operations on a two-shift, 20/7 partial "lights-out" basis (it runs unattended during the night) — the operator sets up the machines at 6 PM and checks them at 9 PM, then both machines run unattended through the night until 7 AM.[730]
- In Clermont-Ferrand, France, international headquarters of Michelin (the world's largest tire manufacturer), a "new and secretive plant" went online in early 1994, producing tires with an integrated system of automation so advanced that rival companies "rushed to check out the patents." Michelin would not reveal the factory's capacity, but it employed only fifty workers, the factory design being described as approaching the futuristic vision of a "lights out" factory.[731]
- For two decades semiconductor manufacturers have dreamed about lights-out chip fabrication plants. There have been some respectable attempts to achieve this goal in the past, but the high cost of systems integration prevented their widespread adoption. Today, the required increase in equipment usage and the required reduction in process variation and contamination is driving "fab" automation levels closer to 100%.[732]

Although a number of totally automated production lines have been attempted, "appropriate automation" was still a more cost-effective solution than "total automation" in 2004. Some claim that no matter how automated a factory becomes, humans will still be required to perform those functions not easily automated, including supervision, decision-making, maintenance and troubleshooting, as well as complex assembly operations.[733,734] However, assembly of simple precision products such as electronics (e.g., circuit card assemblies) and many high-volume assembly tasks for well-understood processes (e.g., the use of pick-and-place robots for electronic component insertion, robotic riveting, or automated sealing) normally permit a high degree of automation and achieve high quality. There are also many successful high-speed continuous assembly lines making such products as diapers, camera film, or

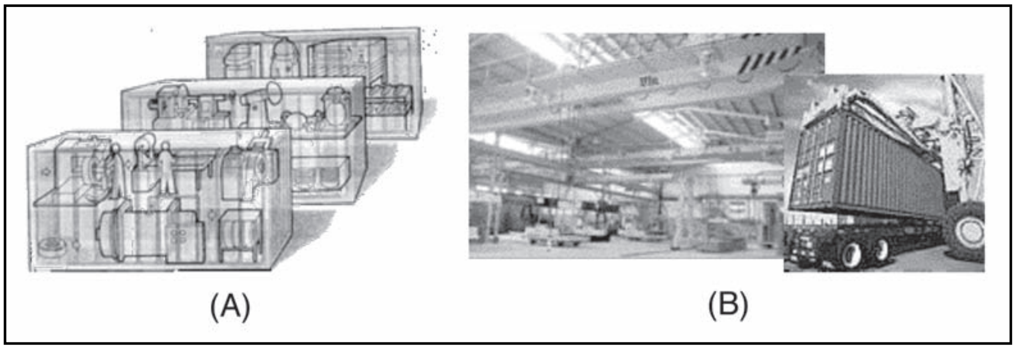


Figure 3.15. Production mini-plants and assembly plant for production mini-plants. (A) SciNet Mini-Plants. (B) SciNet Assembly Plant for Mini-Plants. (courtesy of SciNet[791])

fabric softener sheets wherein the product may be generated at hundreds of meters per minute. But electromechanical assembly (e.g., wiring harness routing, optics/frame mounting, and sensor integration) remains largely manual. The barriers to increasing the speed of assembly are bottlenecks or transformation points, where the assembly line must slow down or even stop suddenly if there is a problem.[734]

Additionally, while some assembly lines may be highly automated, the creation of these automated processes is not automatic. Most robotic assembly processes are product- and process-specific and must be custom-developed and debugged.[734] There are as yet few "design for assembly" (DFA) tools that use robust, structured assembly process models to provide the best assembly knowledge to the design and manufacturing team. Part of the problem is that current CAD assembly modelers have only a limited perception of spatial relationships, which enables the creation of process plans that incorporate tasks which are physically impossible to perform or that require the creation of custom tools. Today's "general-purpose" assembly systems are limited to performing the same process for similar products, with modification of programming and specific tooling. As industrial engineers gain better scientific understanding of component materials, product designs, and manufacturing processes and equipment, it is believed that automated assembly will become easier and less expensive.[734] These engineers are also beginning to explicitly analyze the impact of self-replicating robots on the mix of automated and manual operations in the context of industrial automation systems,[735,736] communication and control for self-replicating robots,[737] and also on emerging concepts of "industrial ecology".[738-745]

A comprehensive survey of the last three decades of advances in manufacturing technology[746] and factory automation is beyond the scope of this book, but a great deal of progress has been made in automated parts fabrication via CAD/CAM/CAE,[747-752] intelligent manufacturing systems,[753-756] flexible assembly systems,[757-759] flexible manufacturing systems,[760-768] automated work cells and computer-integrated manufacturing (CIM),[769-779] automated planning including agoric systems[780-783] and other means (Section 5.7), and "self-formation" in manufacturing.[784-788] The historical development of control structures in automated manufacturing is reviewed by Dilts et al.[789]

Finally, we might also consider to be self-replicating a factory system which contains all of the tools and component machines necessary for its own manufacture, but which requires human operators (hence lacks only process control closure). One example which approaches this class of self-replicating system is the production mini-plants (Figure 3.15(A)) in mobile containers marketed by Science Network (SciNet).[790] These 40-foot containers are 2.5 m x 2.5 m x 12 m in size (30 m^2 floor space) and are designed to be supplied to developing countries that need to install a quick turnkey-type manufacturing capacity for bakeries, tire retreading, or mobile medical units. All production machinery is fixed on the platform of each mini-plant system container, with all wiring, piping, and installation parts included. SciNet also has designed a shippable prototype assembly plant[791] with 3060 m^2 of (mostly open) floor space (Figure 3.15(B)) that can also be supplied to the host country at a cost of $3.2M and then can be used to manufacture more than 700 different kinds of mini-plants,[792] including mini-plants for making cutting and machine tools, concrete pipe, industrial and water valves, steel nails, bricks and concrete blocks, welding electrodes, electrolytic coatings, concrete mixing, grey iron smelting, reinforcement bar bending for construction framework, metal sheeting for roofing and ceilings, manual electrical tools, forceps, plated drums, pressure-forged molded pieces, forged ball bearings, polypropylene, silicon carbide abrasives, plastic boxes, hoists, electrical generators, storage batteries, and electrically welded construction mesh. The assembly plant has a stated production capacity of 1872 mini-plants per year.[792] The literature is silent as to whether the assembly plant can manufacture a sufficient number of different mini-plant types so as to enable the manufacture of a second assembly plant — and hence, to replicate — but, judging from the diversity of mini-plants enumerated above, it does not seem implausible to presume that this could be so.

Hans P. Moravec, a principal research scientist at the Robotics Institute at Carnegie Mellon University, was reported[793] as claiming that "by 2040, robots should be skilled enough to design and build automated factories that manufacture improved versions of themselves. Business competition will ensure that robots take over human jobs until 100% of industry is automated, from top to bottom." In his recent book, Moravec[794] offers more details of the path leading to self-sufficient and self-replicating robots.

In 1995, Raj Reddy, head of the Carnegie Mellon University (CMU) Robotics Institute and co-chair of the President's Information Technology Advisory Committee (PITAC) from 1999-2001, listed "95% self-replicating systems" as one of the "longstanding challenges in the AI area that will be within technological reach in the next twenty years."[7] Reddy lectured on self-replicating systems in 1983 after hearing about the 1980 NASA study (Section 3.13), remains interested in "self-reproducing factories and their necessary conditions",[795] and is associated with the "Automated Machine Shop project" at CMU.[796]

3.8 Macroscale Kinematic Cellular Automata (1975-present)

Rigorous research on kinematic replicators is difficult to execute, but is more useful if one is trying to create a physical working model of a self-replicating system. By contrast, cellular automata (CA), in which mere patterns of bits self-replicate, are more computationally accessible to investigators — the theoretical underpinnings are rigorous and well-understood, the start-up costs are low, and the results are often quickly transferable to software having commercial potential such as genetic algorithms, scientific visualization tools, or simulations of complex systems.[711] But CA have less direct relevance to physical models because a physical implementation would lack the ability to move in physical space, since CA are normally embedded in a fixed tessellation environment. A few researchers have tried to combine these two approaches in an attempt to capture the best of both worlds, in effect adding physical mobility to self-replicating cellular automata.

The first advocates of this approach were cellular theorists who started with cellular automata and "kinematicized" them. One of the earliest proponents was Richard Laing, who in a series of papers[559-561] during 1975-1977 proposed a "hybrid cellular-kinematic automaton" which would use strings of cells (one dimensional tessellations) to compute and construct more strings — achieving self-replication — by means of a repertoire of simple mechanical actions between the strings, e.g., sliding local shifts of contact, local changes of state, and local detections of such state changes.[561] Laing clearly envisioned the possibility of a macroscale implementation of his scheme[558] when he wrote: "I can see no reason why an electronic engineer could not easily produce the design of electronic componentry having the required properties to implement a system such as I have described....Whether such a system could be realized in terms of biological components as well I do not know." Interestingly, Laing's scheme is primarily a proposal for molecular machines and, as such, is discussed in more detail in Section 4.8, below.

In 1979, CA theorist Armin Hemmerling introduced a model "system of Turing automata" wherein finite automata inhabit a multidimensional tape on which the automata can move around and read and write the tape squares.[797,798] During 1988-89, Goel and Thompson[799-802] introduced a related approach, known as "movable finite automata," involving computational entities able to move around and interact with each other in a fixed lattice, and Lugowski[803] described a "computational metabolism" or "liquid computer" in which roving processors called tiles migrate across a tessellation environment like a liquid, recognizing and reacting to their neighbors. In the mid- and late 1990s, CA theorists continued adding new modes of "movement" to cellular automata. For example, the method of "movable cellular automata"[804-806] allows the modeling of materials properties by treating matter as composed of a 3-D array of neighboring "particle" cells with specific interaction rules; reaction-diffusion phenomena and excitable media can be similarly modeled.[807] Adamatzky and Holland[808] have computationally modeled excitable mobile agents moving on a lattice, or "lattice swarm systems." Sipper[378-380] investigated a 5-cell non-uniform cellular automaton self-replicating loop using cells of atypically high complexity, in a model that allows state changes of neighboring cells and rule copying into them (this latter characteristic can be considered a form of cellular movement). Lohn and Reggia[369-371] introduced a model consisting of movable automata called effector automata, embedded in a cellular space, along with a new method of automata input called orientation-insensitive input, and others have investigated mobile automata,[336,809] lattice-unrestricted "graph automata",[810] and distributed assembly of 2-D shapes.[811-814]

In the 1990s, a second wave of advocates appeared — robotics engineers whose training would normally predispose them to the kinematic approach for machine self-replication. Reversing the earlier approach of kinematizing the cellular automata, these engineers began proposing kinematic robotry that could be "cellularized," in an attempt to simplify the complexities inherent in physical self-replication that von Neumann had first encountered. In his 1996 review, General Dynamics Advanced Information Systems research engineer Tihamer Toth-Fejel[711,815] aptly termed all these attempts "kinematic cellular automata" or KCA. Such automata would consist of many identical mechatronic modules, organized into a dynamically reconfigurable system and implemented in the physical world.

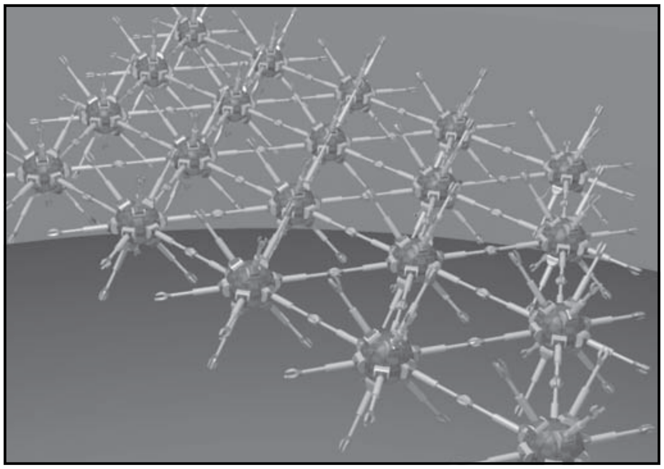


Figure 3.16. Hall's "utility fog" foglets.[820] (courtesy of J. Storrs Hall)

It would take a relatively large number of identical KCA cells to make up a physical replicator. With conventional cellular automata, the individual cells cannot move and can only change state, and patterns move across a static array. In contrast, the KCA mechatronic design allows individual physical cells — not just patterns — to move with respect to each other, permitting the physical swarm to change shape just like the virtual patterns in cellular automata. Because they are derived from the CA field, KCA aggregates have the advantage of being more naturally fault tolerant and more flexible than non-modular or unitary kinematic robots, and the KCA are more structured in the interactions between individual cells. (Principal disadvantages are that the individual KCA cells must be fairly complex, compared to the typical unitary kinematic machine "part," and that in most designs the KCA aggregate is not capable of manufacturing its own component cells from more primitive parts.)

Proposals for KCA replicators typically envision a very large number of basic cell units operating in parallel, that can replicate a given geometric or lattice arrangement of those same cell units. Confirmed early design proposals (many of them apparently independently conceived without direct knowledge of the others' work) include Kokaji's "fractal mechanism" work at AIST in 1988,[817] Hall's well-known utility fog* with 100-micron "foglet" robots (Figure 3.16) in 1993-1995,[818-820] Chirikjian's "metamorphic" robots[1281] in 1993-1994, the "Fractum" self-repairing machine at AIST during 1994-1999,[821-823] Michael's fractal robots or "programmable matter" (Figure 3.17) in 1994-1995,[816,824] Hasslacher and Tilden's "self-assembling colonies of micron-scale biomorphic machines" in 1994-1995,[185] Bishop's XY active cell aggregates

---

** The American inventor Thomas Alva Edison apparently anticipated at least a part of the functionality of utility fog at a dinner talk[834] as long ago as 1890: "...as if out of a great revery, saying what a great thing it would be if a man could have all the component atoms of himself under complete control, detachable and adjustable at will. 'For instance,' he explained, 'then I could say to one particular atom in me — call it atom No. 4320 — "Go and be part of a rose for a while." All the atoms could be sent off to become parts of different minerals, plants, and other substances. Then, if by just pressing a little button they could be called back together again, they would bring back their experiences while they were parts of those different substances, and I should have the benefit of the knowledge.'" Following this, Landers[835] discussed modular building block based robots in 1966, Erber et al[836] studied pattern replication in arrays of magnetic blocks in 1969, Toffoli and Margolus[332] in 1987 and Rasmussen et al[368] in 1992 wrote of "programmable matter" in a slightly different context, and Okuma and Todo[837,838] analyzed assembly methods using cubic blocks as primitives at least as early as 1993.*

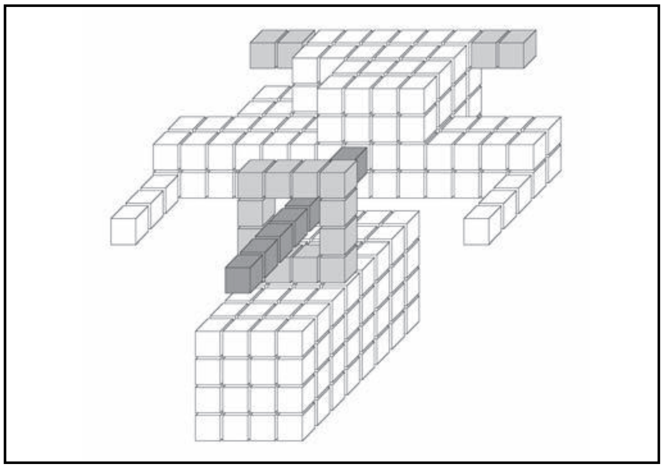


Figure 3.17. Michael's Fractal Robots. (courtesy of Michael[816])

or ACA (Figure 3.18) in 1995-1996[825-828] (Section 4.12), Toth-Fejel's KCA cells in 1995-1996,[815] Freitas' programmable surfaces in 1995-1996,[2886] and the replicating swarm of Globus et al[224] in 1997-1998 (Figure 3.19), plus one unconfirmed report that Thorson[829] described "assemblies of tiny machines that flexibly coordinate to form human-scale objects" in 1991.* Only one of these proposals, by Bishop[828] (Section 4.12), envisioned additionally the assembly of individual KCA cells from more primitive parts (Figure 3.20), thus extending the capability of the KCA replicator concept beyond the mere replication of selfsame building-block patterns. However, Yim et al[830] have alleged that microscale KCA systems built from cubical modules (as in the schemes of Michael and Bishop) might have significant disadvantages, for example, in that "rolling/rotational motions are preferable to sliding motions because they can have less friction, which becomes very important as systems scale down in size." Chen[831-833] also studied modular reconfigurable robotic system assembly configurations in the early 1990s.

The experimental field of modular robotics (that could enable the physical realization of the aforementioned theoretical KCA replicators) has exploded in recent years, with many new designs proposed and a number of prototypes built in hardware, starting in the late 1980s and early 1990s. One of the earliest examples was the cellular robotic system (CEBOT) pursued by Fukuda's group[841-849] in Japan, starting in 1987. CEBOT is a dynamically reconfigurable robotic system composed of diverse robotic cells combined in different configurations. Each cell-robot is autonomous and mobile, able to seek and physically join other appropriate cells. Fukuda has used CEBOT (and more recently MARS or micro autonomous robotic system[850]) to investigate multi-purpose end-effector systems,

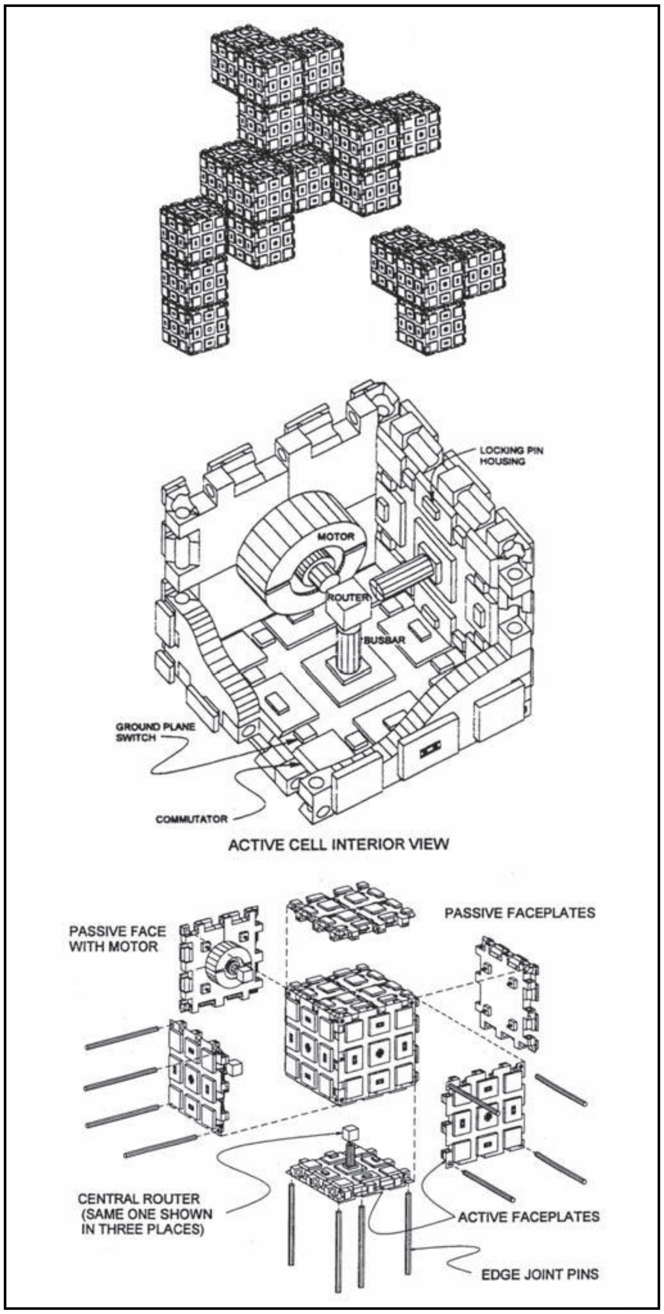


Figure 3.18. Bishop's XY Active Cell and Cell Aggregate.[827,828] (courtesy of Forrest Bishop)

---

* *Toth-Fejel[815] speculates that the use of microscopic KCA cells could explain some of the capabilities of the sometimes human-shaped, liquidlike, evidently nanotechnology-based[825,839] fictional T-1000 robot in the science fiction movie* Terminator 2[840] *— who, Toth-Fejel opines[815] (after discussions with Bishop[825]), could have survived its fall into the vat of molten steel in the final scene by making fuller use of its own technology, as follows:*

1. *Balance-sensors and accelerometers in undamaged areas of the robot sense that it is about to fall, causing a pre-programmed panic sequence to order a lowering of the center of balance and an extrusion of micro or macro hooks from the feet into the floor.*
2. *The same sensors detect the weightlessness of falling, and the pre-programmed panic sequence orders the KCA cells to form into a parachute; hot air rising from the molten steel lifts the robot out of harm's way.*
3. *Depending on the degree of central control required (given that the T-1000 was damaged and degrading fast), the robot could have sprouted wings and glided to safety.*
4. *Upon contact with molten steel, temperature sensors actuate a pre-programmed panic sequence to quickly reconfigure refractory-material cells at its surface into a foamy air-trapping structure, providing the same heat insulation qualities as space shuttle tiles; since molten steel is quite dense, and the machine appears not to be made of solid polymetal (otherwise its weight would have broken through most transportation vehicles, second-story floors, elevators, etc.), the robot could have simply walked across the surface of the vat, to safety.*
5. *Force sensors keep interconnection mechanisms between cells from damage by ordering cells to disconnect whenever the strain gets too high, thus dissipating the energy of bullets over time and distance (something like shooting at gelatin) rather than allowing bullet impacts and deformations as shown in the movie.*
6. *Miniaturized radar systems (already available today) detect the incoming explosive bullet with enough accuracy to predict its trajectory, allowing portions of the T-1000 along that path to slide aside so the bullet passes unimpeded through the robot, eliminating the need to dissipate the kinetic energy of the bullet.*
7. *An onboard cell-fabricating facility allows the robot to exploit the existing industrial infrastructure to make more KCA cells, both for self-repair (by replacing damaged cells) and for self-replication (thus overwhelming any non-replicating opponent).*

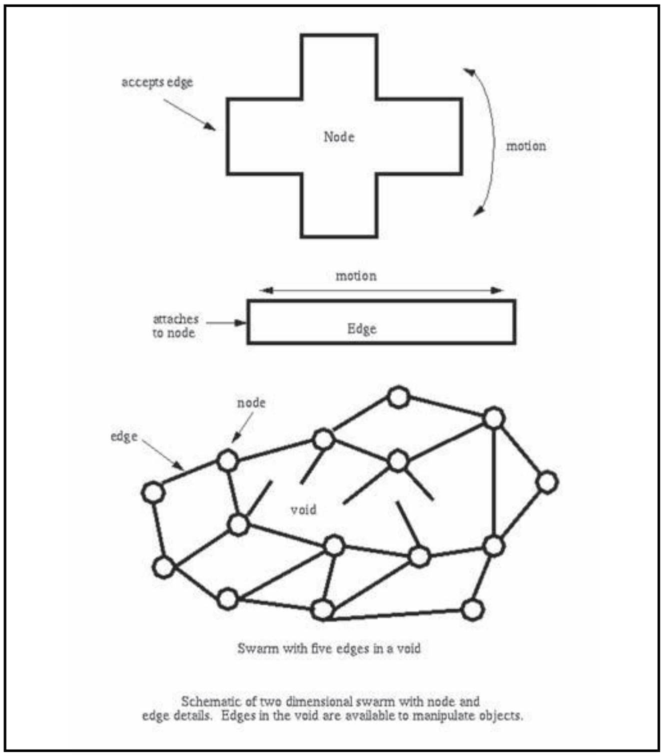
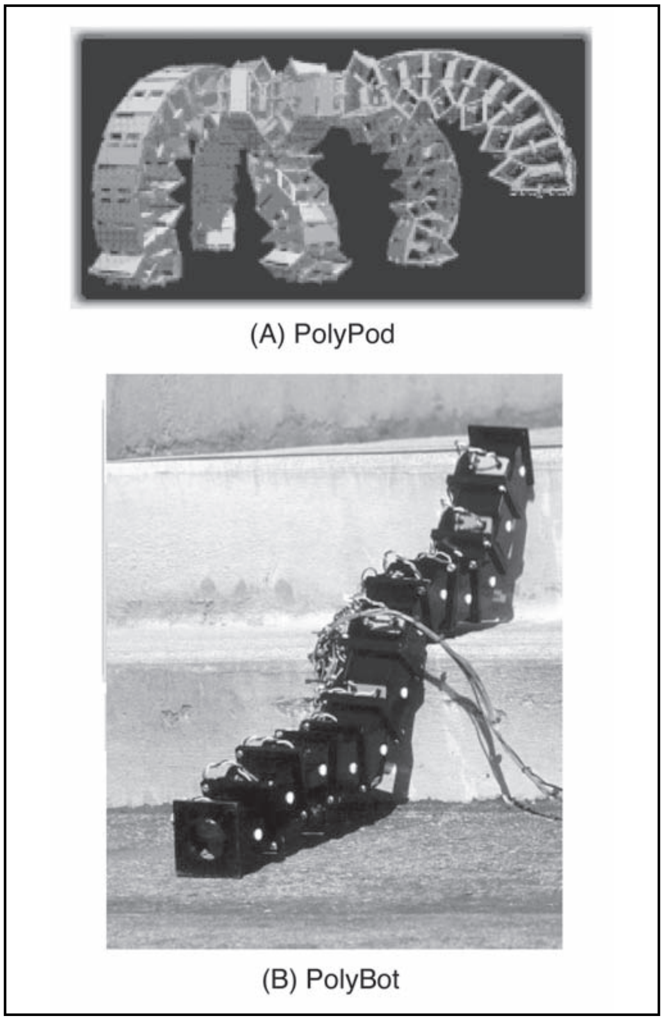

accepts edge
Node
motion
motion
attaches to node
Edge
node
edge
void
Swarm with five edges in a void
Schematic of two dimensional swarm with node and edge details. Edges in the void are available to manipulate objects.

Figure 3.19. “Replicating swarm” of Globus et al.[224]

self-organization, self-evaluation of robot cells, communication among robots, and control strategies for group behavior.[603]

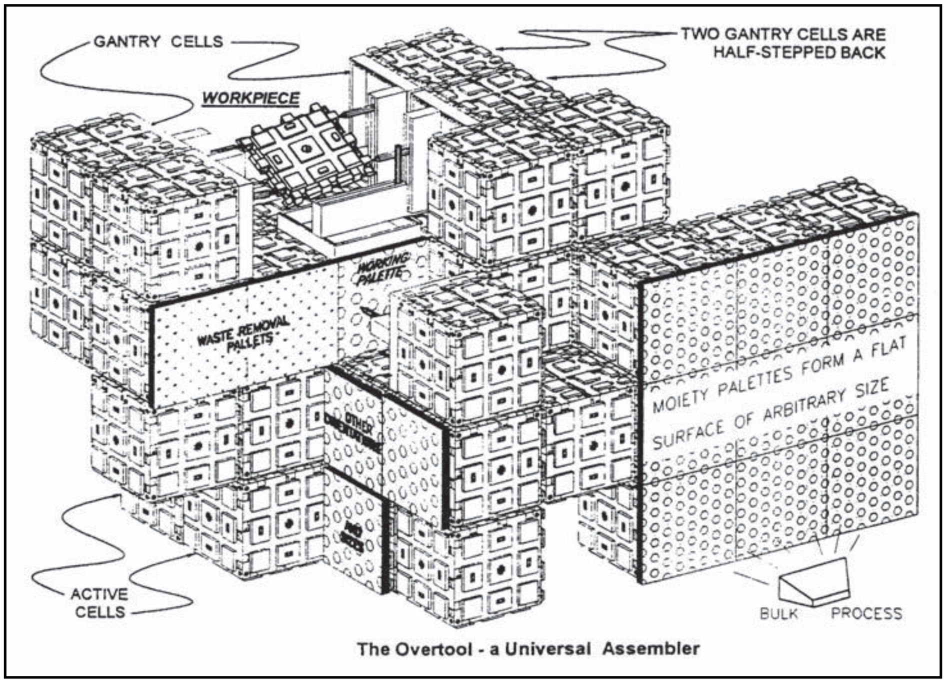
Mark Yim and colleagues[853] designed and built multi-robot polypods[851,854] at Stanford in 1993-1994 (Figure 3.21(A)), continuing in 1998-2001 with polybots[852] for DARPA at Xerox PARC (Figure 3.21(B)). Yim’s polybots are capable of significant physical reconfiguration with some teleoperation assistance from human operators (Figure 3.22), though of course they cannot build new primitive units from smaller components. In between these efforts, Yim’s group briefly pursued “a self-assembling robotic system


(A) PolyPod

(B) PolyBot

Figure 3.21. Yim’s (A) PolyPod multirobot automaton[851] and (B) PolyBot multirobot automaton in snake mode.[852] (courtesy of Mark Yim and Xerox PARC)

Figure 3.20. Bishop’s proposed “Overtool” would assemble individual KCA cells from more primitive part.[828] (courtesy of Forrest Bishop)


GANTRY CELLS
TWO GANTRY CELLS ARE HALF-STEPPED BACK
WORKPIECE
WORKING PALETTE
WASTE REMOVAL PALLETS
MOIETY PALETTES FORM A FLAT SURFACE OF ARBITRARY SIZE
ACTIVE CELLS
BULK PROCESS
The Overtool - a Universal Assembler

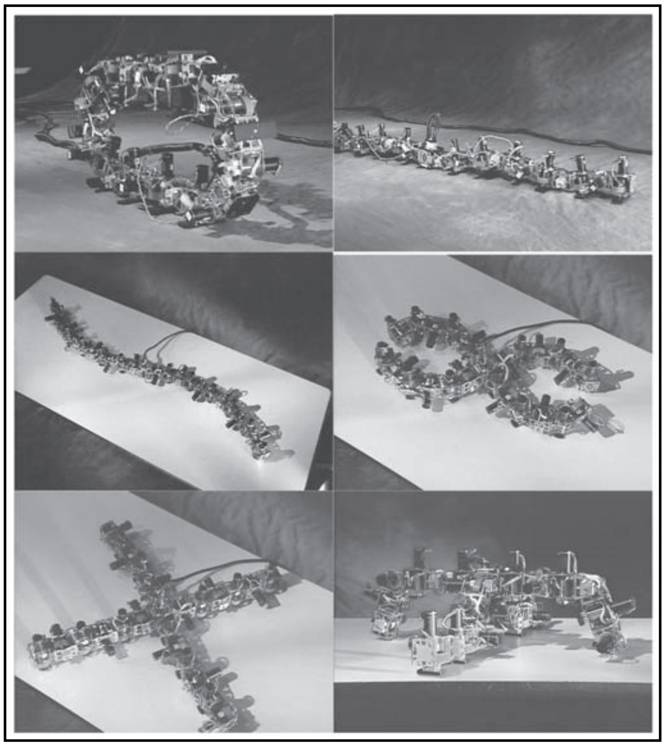


Figure 3.22. Yim's PolyBot multirobot automaton reconfigures itself from loop to snake to spider mode.[852] Twenty-four Generation II modules were used to demonstrate reconfiguration from a snake to a four legged spider form. Docking was aided by teleoperation, though latching and unlatching was automatic. (courtesy of Mark Yim and Xerox PARC)

capable of approximating arbitrary three dimensional shapes utilizing repeated rhombic dodecahedron shaped modules," and demonstrated algorithms which, at least in simulations, transformed a square plate of 441 modules into a teacup shape in 1808 steps and 625 modules into a hollow sphere in 3442 steps.[830] Hardware prototypes of these "polymorphic cytokinetic quasi-fluid crystallic robots"[855] (so-named somewhat tongue-in-cheek, according to the researchers) were reportedly under construction in 1997,* with each robot module to have 48 shape memory alloy actuators including 24 for edge motion rotations and 24 in six groups of four to achieve dynamic shape modification.[830]

Yim and colleagues in the Xerox PARC modular robotics group have also produced 3-D "telecube" modules (Figure 3.23)[858-865] which are cube-shaped modules 5 cm on a side with faces that can telescope outward by 36-40 mm, thus doubling the length of any dimension while applying a thrust force of ~12 N. Each face can contract (Figure 3.24(A)) or expand (Figure 3.24(B)) independently, with a reversible magnetic latching mechanism to attach or detach from any other face of a neighboring module with a holding force of ~25 N, sufficient to resist a torque of 0.75 N-m between adjacent cubes. To reconfigure a telecube lattice (Figure 3.24(C)), a module at one site on a virtual grid detaches from all modules except one. By extending (or contracting) the faces that are attached to it, the module moves to the neighboring site.

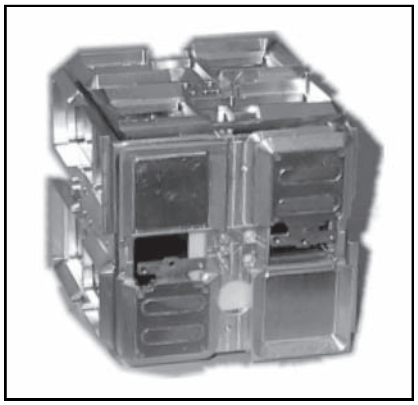


Figure 3.23. A Telecube G2 module fully contracted. (courtesy of Xerox PARC[861])

Chirikjian[1281-1283] and Murata et al[821] have separately simulated and built planar hexagonal robots that roll around each other. While neither addressed experimentally the decentralized self-assembly of arbitrary 3-D shapes,[830] Chirikjian's vision of self-reconfigurable[867] or "metamorphic"[1281] robots (at the Johns Hopkins University Robot Kinematics and Motion Planning Lab[868]) clearly anticipates this: "A metamorphic robotic system is a collection of mechatronic modules, each of which has the ability to connect, disconnect, and climb over adjacent modules. A change in the macroscopic morphology results from the locomotion of each module over its neighbors. That is, a metamorphic system can dynamically self-reconfigure. Metamorphic systems can therefore be viewed as a large swarm of physically connected robotic modules which collectively act as a single entity." (Freitas' "metamorphic surfaces" concept (*Nanomedicine,*[228]

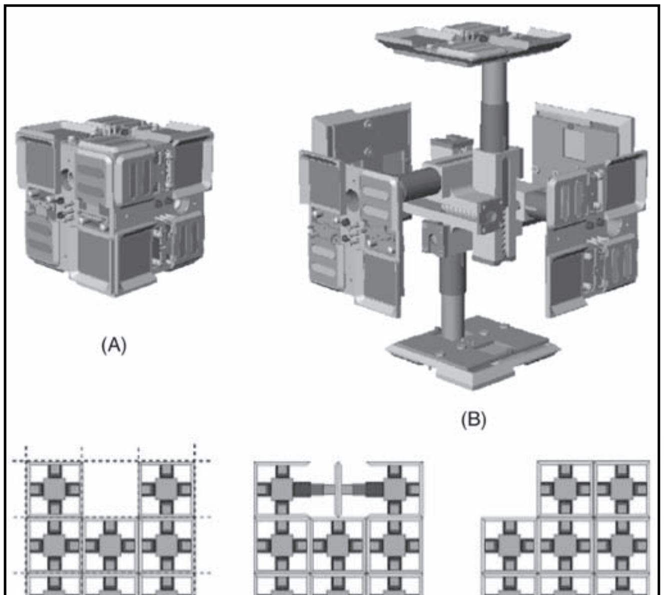


Figure 3.24. Telecube configurations and lattice movement. (A) Telecube collapsed. (B) Telecube expanded. (C) Reconfiguration of a lattice of 8 telecubes via sliding motions. (courtesy of Xerox PARC[861])

** According to Tad Hogg,[856] this design turned out to be too complicated (needing actuators for 12 faces) and was not continued to any functional hardware, although a few passive devices with magnets were built that a person could manually reconfigure to illustrate how such robots would work if they were ever built. Hristo Bojinov was instrumental in simulations involving local controls, as opposed to a high level controller that told each module where to go. The simulation results with these robots, e.g., making branching structures, growing around objects, etc., are described in Bojinov et al,[857] and nicely illustrate the contrast between broadcast control and local control.*

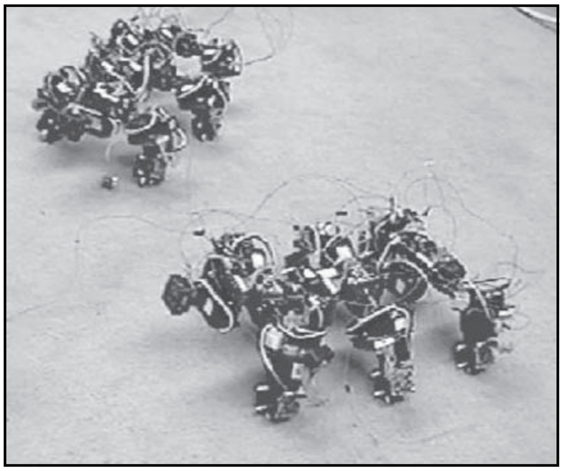


Figure 3.25. CONRO multirobot system (20 modules making two hexapods) (photo courtesy of USC Information Sciences Institute).[866]

Chapter 5) in the medical nanorobotics field is similar.) Michael[869] has constructed several simple operating prototypes of his cubical "fractal robots" design, using blocks 12 inches and 5 inches in size. The "Fractum" machine developed at AIST[823] is claimed to be the first modular mechanical system to demonstrate self-repairing capability using more than ten modules. Other modular mechatronic robotic systems include:

- CONRO (Figure 3.25) at USC/ISI;[866]
- the Crystal Robot,[871-874] Molecule Robot,[875-877] and the "desktop mobile manipulators"[877] at the Dartmouth Robotics Lab;[878]
- 3-D modular units for self-assembly of desired shapes (Figure 3.26) at the Mechanical Engineering Laboratory in Japan,[822,870] a kind of macroscale utility fog (cf. Figure 3.16);
- the LEGO®-based autonomous robot teams (MinDART) at the University of Minnesota;[879]
- the tetrobot modular reconfigurable robot at Rensselaer Polytechnic Institute;[880-884]

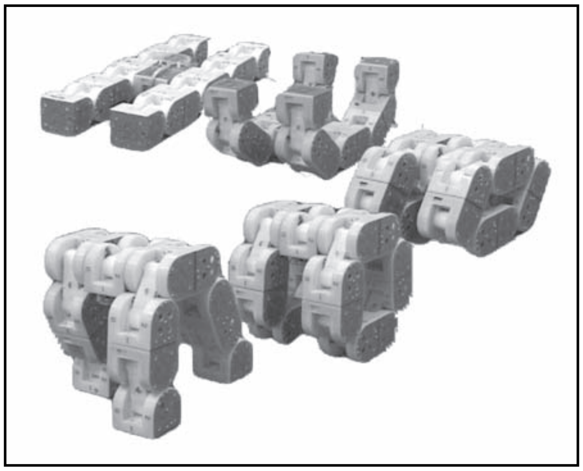
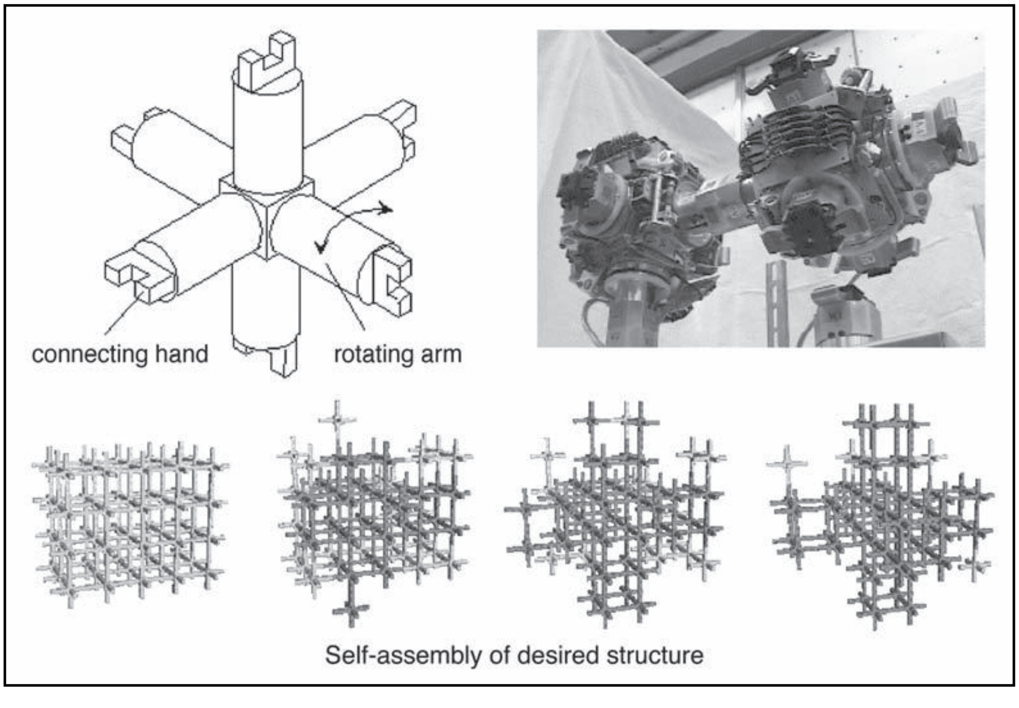


Figure 3.27. Modular self-reconfigurable robot M-TRAN (Modular TRANSformer) changes its shape from a crawler to a four-legged walking robot. (courtesy of Intelligent Systems Institute, National Institute of Advanced Science and Technology (AIST)[887-889])

- the reconfigurable modular manipulator system (RMMS) of the Advanced Mechatronics Laboratory at Carnegie Mellon University;[885]
- the DARPA Microrobot Project at Michigan State University;[886]
- the modular self-reconfigurable robot M-TRAN or Modular TRANSformer[887-889] (Figure 3.27) from the Intelligent Systems Institute, National Institute of Advanced Science and Technology (AIST);
- a miniaturized modular machine system using shape memory alloy, also at AIST;[890-892]
- the European Swarm-bots Project;[893]
- the Linux radio robot, solarbot, and ant-like robots of the Intelligent Autonomous Systems Engineering Laboratory of the University of the West of England;[894]

Figure 3.26. Distributed self-reconfiguration of 3-D homogeneous modular structure (courtesy of Intelligent Systems Institute, National Institute of Advanced Science and Technology (AIST)).[870]



- the HYDRA Project of the Artificial Intelligence Laboratory at the University of Zurich;[895]
- the Amoeba Robot project at the Autonomous Systems Engineering Laboratory at Hokkaido University;[896]
- the Random Morphology Robot Project at the University of Dortmund, Germany,[897] and the self-reconfiguring robots for morphogenesis of Hosokawa et al;[898]
- the PIRAIA Project at the Swedish Institute of Computer Science;[43]
- a large number of other modular snake[899-901] and segmented[902] robots; and
- the ICES Cubes or I-Cubes system (Figure 3.28) at the CMU Robotics Institute, a collection of independently controlled mechatronic modules (links) and passive connection elements (cubes).[903-905]

Closely related research areas such as distributed robotic systems,[906,907] multirobot systems,[906,908] and swarm robotics generally[909-913] may also be relevant but are beyond the scope of this book.

Another interesting project in 1995-1996 was the development of a computer-controlled LEGO® factory — itself made entirely of LEGO® components — that could build LEGO® cars. The LEGO® factory project was conducted at the CODES Lab in the Electrical and Computer Engineering Department at the University of Massachusetts[914] and began as an Electrical Engineering senior design project inspired by a similar project at Linkoping University, Sweden. The effort was supported by an NSF grant and involved at least 7 students and 5 professors from the University of Massachusetts, Boston University, and Harvard University. The factory (Figure 3.29) was computer-controlled, incorporated up to 16 sensors and a number of motors, and assembled the LEGO® cars in 7 steps. The factory is "an interesting demonstration of a simple, small-scale system capable of handling and assembling the same type of parts that make up the system."[915] The students' future plan[914] was to add "decision-making functionality and the ability to flexibly manufacture multiple products," although the explicit pursuit of self-replication was never stated as a goal before the project ended. The factory itself was not capable of self-replication.* A LEGO® model of a steel production factory has also been done in the "Lego Lab" at the University of Aarhus.[916]

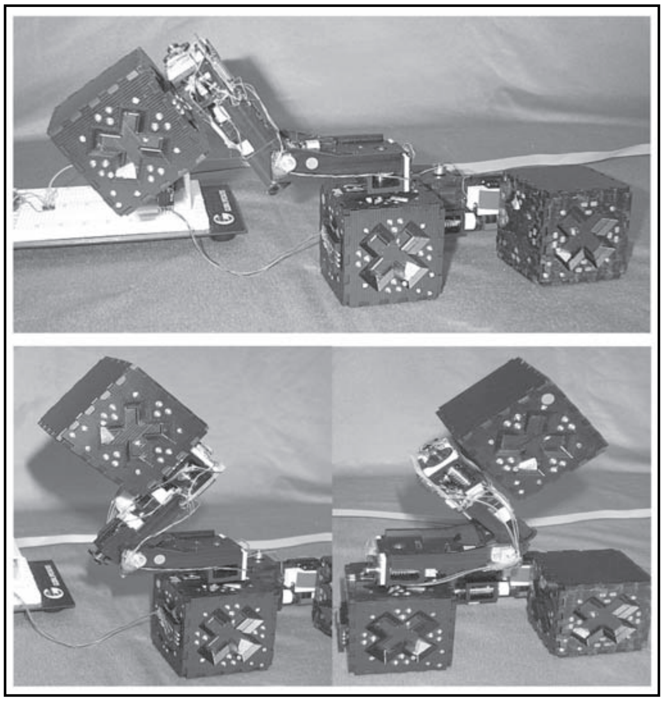


Figure 3.28. I-Cubes: A modular self-reconfiguring robotic system. (courtesy of CMU Robotics Institute[903])

LEGO® is becoming popular for mechatronics hobbyists.[918] Other LEGO®-based replicator projects are currently underway (Sections 3.22 and 3.23) and one of these has succeeded in building the first LEGO®-based self-replicating machines (Section 3.23). The

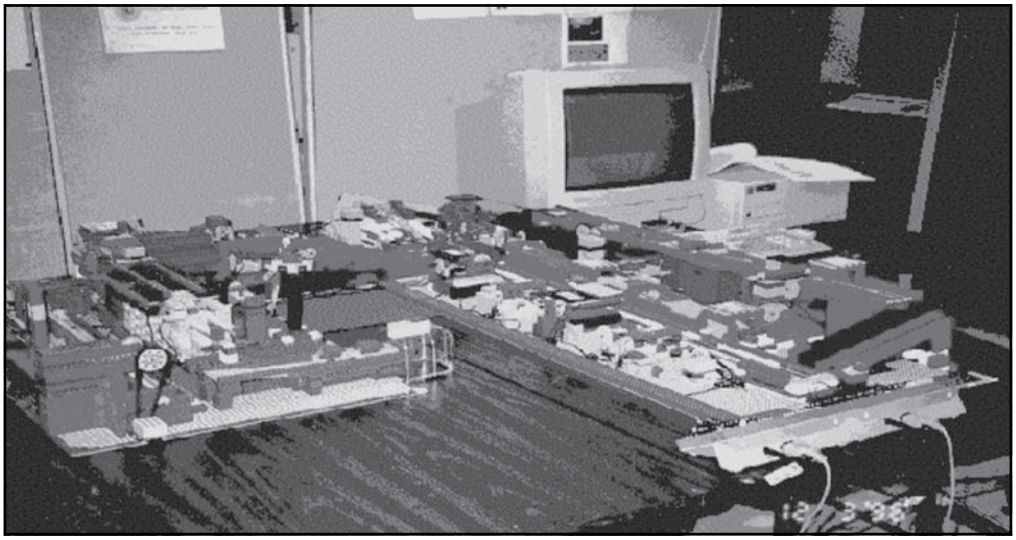


Figure 3.29. Computer-controlled LEGO® car factory made entirely from LEGO® components. (courtesy of University of Massachusetts)[914]

authors are unaware of any similar efforts using other popular minimal parts-set construction toys* such as Erector®[919] or Meccano®,[920] although in 1975 a mechanical computer that could play tic-tac-toe was constructed at MIT[921] using Tinkertoys®.[922]

---

* *The first mention of this possibility in the literature appears to have been made by Mitchel Resnick, who concluded his 1987 discussion[917] of LEGO®-based robotic simulated animals with the following comment: "Eventually (and more speculatively), LEGO®/Logo could evolve into a type of universal constructor. One can imagine a LEGO®-based automated factory, in which LEGO® machines construct and program new LEGO® animals — and new LEGO® factory machines. Or, perhaps, the factory machines and the animals should not be viewed as separate categories; perhaps the factory machines are the animals. Obviously, such projects would require complex programs and new types of building materials, including specialized pieces outside of the LEGO® repertoire. Such projects will probably not be feasible for many years — if ever." Just 14 years later, this "not...feasible...ever" project was accomplished experimentally (Section 3.18).*

Toth-Fejel[711] envisions a self-replicating system composed primarily of a robot arm made up of KCA cells. A well-defined grid of KCA components would surround the replicator, with each cell containing sensors, actuators, and a central processor, all of which could be simulated at a kinematic level. The next step would be to build a working prototype, using stereolithography or similar rapid prototyping techniques.[927-933] To achieve further cost reductions, off-the-shelf parts would be used whenever possible to build physical prototypes. Toth-Fejel recommends starting a KCA development effort with simulations involving a very rich environment of parts. In other words, the entropy of the surroundings, the number of parts that make up the replicator, and the number and complexity of the assembly steps should all be minimized, while the complexity of the parts themselves should be maximized. After success is achieved using the initial replicator in a rich environment, the number of parts and assembly steps should be doubled in the replicator, while the complexity of each part in the environment should be halved, and self-replication again attempted. This iterative process should then be continued (in the manner of Moore's Law in semiconductor chip design), until either complete success is achieved or insurmountable obstacles are encountered, with the goal of working toward complete KCA autotrophy in which the replicator can assemble itself from the most primitive KCA cell components. Once such componential autotrophy is achieved, the next task would be to find molecular analogs for all the components, and work towards true molecular autotrophy while respecting public safety guidelines (Section 5.11). In keeping with the idea of approximating the real world with greater detail, the amount of disorder in the environment should also be increased as the experiments progress.

Much like the ideal array of individual nanorobots comprising the programmable dermal display proposed in 1999 by Freitas (*Nanomedicine*,[228] Section 7.4.6.7), Tilden and Lowe[936] have suggested that "it is potentially feasible to manufacture nanorobots that are capable of sophisticated symmetric behaviors, either through independent function or by assembling themselves into collective units....for example, high-resolution video screens that can repair themselves simply by having a microscopic robot at each screen element. These 'pixelbots' would be capable of producing light, but smart enough to remove themselves from the video array should they ever fail. Other pixelbots would sense the vacancy left by any defective device and reorganize themselves to fill the hole." Such arrays could replicate patterns in the manner of cellular automata.

Hasslacher, Tilden, J. Moses and M. Moses[185,937-940] have investigated "autonomous self-assembling robotic mechanisms" in the context of groups of robots of various different species that vie for control of energy resources in order to "survive." In 1994, Hasslacher and Tilden[185] (Section 5.1.3) operated a Robot Jurassic Park (Figure 3.30) "where over 40 robots of 12 different solar powered species have been running continuously for over 6 months....There has been evidence of flocking, fighting, cooperative group battles against particularly aggressive forms, even pecking-order dominance, but little in the way of true cooperation that would indicate hive structure stability for such devices....Further work would have to be done in sensor technology so that like creatures would be able to recognize others of their own hive." During 1995-6, Tilden (with Moses)[937-939] operated their own version of the robotic Jurassic Park in which "new control systems have been devised to allow these devices to power-mine their environment exploiting the available light-energy sources without having to resort to internal batteries. Future work will examine and promote the development of these mobile machine components so that they may act as coordinating organs in sophisticated robots for application-specific tasks, creating a form of 'living LEGO®' with inherent self-repair and self-optimization characteristics." More recent work has found some evidence of primitive territory formation in populations of mobile robots.[941]

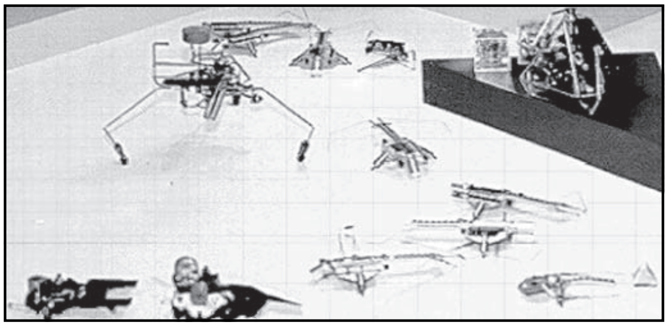


Figure 3.30. A moment in the life of the Robot Jurassic Park. (courtesy of Hasslacher and Tilden[185])

3.9 Space Manufacturing Systems with Bootstrapping (1977-present)

One of the earliest advocates of self-replicating manufacturing systems in space was Freeman Dyson, who, in lectures in 1970 (Section 3.6) and 1972,[2934] observed that space might be a more appropriate venue for replicators than the verdant hills of Earth: "The true realm of self-reproducing machinery will be in those regions of the solar system that are inhospitable to man. Machines built of iron, aluminum, and silicon have no need of water. They can flourish and proliferate on the moon or on Mars or among the asteroids, carrying out gigantic industrial projects at no risk to the earth's ecology. They will feed upon sunlight and rock, needing no other raw material for their construction. They will build in space the freely floating cities that Bernal imagined for human habitation. They will bring oceans of water from the satellites of the outer planets, where it is to be had in abundance, to the inner parts of the solar system where it is needed. Ultimately this water will make even the deserts of Mars bloom, and men will walk there under the open sky breathing air like the air of Earth."

Following the publication of papers and books[942-945] on the colonization of space by physicist Gerard K. O'Neill (1927-1992)[946] and others[947-951] in the mid-1970s, the potential utility of manufacturing in space using nonterrestrial materials (materials found in

---

** There have been over 500 imitations of Erector® and Meccano® in over 40 countries[923] (with at least 10 still being made today), including[923-926] American Model Builder, Ami-Lac (Italy), Bing's Structator (Germany), BRAL (Italy), Buildo, Construction C10, Construct-O-Craft, Elektromehaniskais konstructors (Russia), Exacto (Argentina), Ezy-Bilt (Australia), FAC (Sweden), Junior, Lyons, Make Your Own Toys, Marklin Mehanotehnika (Slovenia), Metall (Germany), Mekanik (Sweden), Mek-Struct (China), Merkur (Czech., renamed Cross), Metallus, Mini Meta-Build (India), Modern Morecraft, Necobo, Palikit, Pioneer, Primus Engineering Outfits (England), Schefflers, Stabil (Germany), Steel Engineering (U.S.), Steel Tec (China), Stokys (Switzerland), Structo (U.S.), Structomode, TECC (Czech.), Teknik, Takno (Norway & Denmark), TemSi (Netherlands), Thale Stahlbau Technik (E. Germany), The Constructioneer, The Engineer (Canada), ToyTown, TRIX (Germany), Trumodel (U.S.), Vogue (England), Wisdom/Sagesse (China), and ZigZag. Other less-popular construction toys[926] include American Plastic Bricks, Anker, Bayko, BILOFIX, Blockmen, Brik-O-Built, Brio, Bristle Blocks, Builderific, Cuburo, CoinStruction, Constux, Easy Fit, Eitech, Fiddlestix, Fischer Technik, Fractiles, Frontier Log Building, GEOMAG, Hexlo, Expandagon, ImagiBRICKS™, JOVO, KAPLA, Knex, LASY, Liberty Logs, Lincoln Logs, Lokon, Manetico, MegaBloks, Nice-Dice, Plastikant, PlayMobile, Quadro, Rhomblocks, Richter's Anchor Blocks, Robotix, Rokenbok, Stanlo, Steelbuilder, Toobers & Zots, Zolo, and Zome System.*

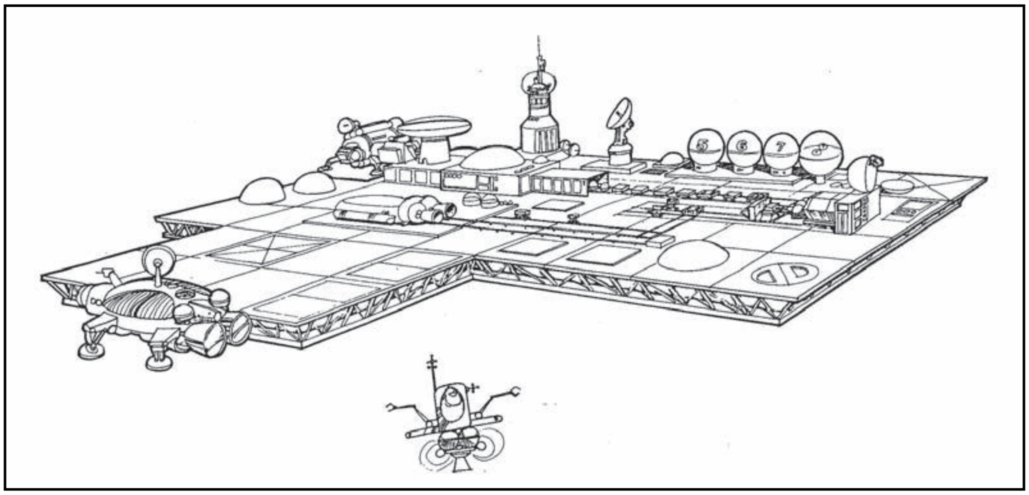


Figure 3.31. Automated space manufacturing facility for the processing of nonterrestrial materials.[962]

space) became clearer. Since the cost per kilogram to reach low Earth orbit even today remains relatively high (~$10,000/kg), it makes sense to search for ways to ship the smallest possible package of manufacturing equipment into space, and then to use that minimal package to gradually expand its own capabilities over the years, a process called bootstrapping that would not require the construction of large monolithic space colonies.[952]

Early proposals advanced by O'Neill in 1977 assumed manned "construction shacks"[948] and made little mention of automation.[947] For example, one proposal[953] envisioned an initial lunar supply base with a mass of "less than 1000 tons, deployed by 25 persons in 4 months, maintained by 10 persons." The buildup rate for industry in space was explored with the assumption that about 3000 tons of equipment would need to be brought up from Earth. These studies[949-951] had included, but only in a limited way, the concept of "bootstrapping": the use of industry in space to yield, as finished products, some components identical to those of the industry itself. Partial self-replication was a key to cost-cutting and to rapid exponential growth of industry in space. Earlier studies[2688,2689] from which the concept of bootstrapping had been excluded had already concluded that 90-96% of the required factory mass could be derived from lunar sources.

The Space Studies Institute (SSI), founded in 1978 by O'Neill to further his research, then turned to the question of reducing the cost of space bootstrapping by resorting to some degree of automation. During 1978-1980, SSI organized a series of workshops[954,2690] aimed at defining more precisely the minimum size of an industrial facility capable of processing lunar materials into pure elements to serve as feedstock for industry in space. The workshops considered scenarios involving manned and unmanned facilities with preliminary estimates of 15-107 tons for partially self-replicating lunar factories of several different types that could grow with a doubling time of 90 days (0.25 year). Instead of the initial cost estimates in the hundreds of billions of dollars, O'Neill found[954,2690] that self-replicating systems "appear capable of achieving high levels of productivity for investments considerably less than $10 billion. They would be in the range of the Alaska pipeline ($7 billion), and much lower than the Churchill Falls, Quebec, electric power system, both of which were private ventures."

Two years after the well-known NASA study on self-replicating lunar factories (Section 3.13) was published, in 1984 O'Neill stated in a book[955] that within about four years SSI would release plans for a space program including self-replicating space manufacturing facilities. Hewitt claims[956] these plans never materialized, but that he published[957] "a logistic analysis of such programs, similar to what SSI had intended." However, SSI notes[958] that in 1988 "the Institute conducted its third major systems study which, in particular, looked at opportunities to bootstrap space industry from low-Earth orbit to the lunar surface as a prelude to large-scale space industrialization." The results of this study were published by the Lunar and Planetary Institute in 1988.* [959]

As for autonomous self-replication, the SSI workshop[2690] judged that "it would be uneconomical and unnecessary to push artificial intelligence to the limit of total machine autonomy, because…a great many jobs can be controlled by humans on Earth, through radio/video links…The indispensable person in space will be the repairman, and it is going beyond present technology to think of replacing him — in every eventuality — by another machine." An extensive multi-year study published by Criswell[961] in 1980 showed that it was extremely likely that self-contained automated processing plants could produce 99% pure elements and large quantities of oxygen from lunar soil, and the 1980 NASA Summer Study (Section 3.13) provided an opportunity to begin defining the precise nature of a "starting kit"[962] for an orbital space manufacturing facility for the processing of nonterrestrial materials (Figure 3.31). The ARAMIS study[963,964] during 1981-1983 investigated additional specific methods for automating space manufacturing tasks, including especially the use of teleoperation or telepresence. Other studies of various concepts for automating assembly operations in space,[965-967] autonomous systems theory,[968] planting robotic "seeds in space",[969] teleoperated microrobots,[970] and bootstrapping space industry[957,1063] or solar power satellite production[1007,1008] with varying degrees of

---

** O'Neill was still interested in replicating systems as late as 1990, when he wrote,[960] under the subtitle "Manufacturing Economically Productive Structures in Space: Self-Replication of General Purpose Production Machines," the following recommendation for the decade ahead: "In its early application in space, self-replication is likely to be employed for three general purpose facilities: mass-drivers, processing plants to generate industrial feed-stock from lunar materials, and general purpose, teleoperated 'job shops' capable of building more mass-drivers, processing plants and job shops. As noted earlier, it is not cost effective to carry self-replication to the 100% level. Many of the components of all three types of facilities are complex but light in weight and therefore inexpensive to lift from the Earth. Self-replication should be confined to the heavy, repetitive components of the production facilities. The logic of self-replication for production facilities in space is that a 'seed' facility consisting of a mass-driver, processing plant and job shop on the Moon and a processing plant and job shop in space could replicate itself in the sequence 1, 2, 4, 8, 16... A series of seven doublings, starting with an initial set of facilities built on the Earth and weighing less than fifty tons, would lead to the capability of processing about 100,000 tons of lunar material per year into completed structures in space. Because of its urgency in terms of potential payback and its derivation from already existing scientific work and profitable industrial practice, a realistic time scale for the earliest pilot plants which are partially self-replicating industrial systems on the Moon and in space is ten years — the year 2000. As doubling times would be as short as two months, the years 2002-2005 could yield a full-scale system processing 100,000 tons per year or more."*

self-replication have continued sporadically throughout the 1980s and 1990s to the present day. In 1984, roboticist Hans Moravec[971] wrote enthusiastically: "I visualize immensely lucrative self-reproducing robot factories in the asteroids. Solar powered machines would prospect and deliver raw materials to huge, unenclosed, automatic processing plants. Metals, semiconductors and plastics produced there would be converted by robots into components which would be assembled into other robots and structural parts for more plants. Machines would be recycled as they broke. If the reproduction rate is higher than the wear out rate, the system will grow exponentially. A small fraction of the output of materials, components, and whole robots could make someone very, very rich."

Most recent studies have included minimizing the size of bootstrapping starting kits using freeform fabrication,[997] molecular nanotechnology,[972-976] and architectures for nanotechnology-based space manufacturing systems such as McKendree's "logical core architecture";[975,976] replicators and nanorobotics in space utilization,[977] orbital tower construction,[978,979] lunar development[980,981] and manned mission support;[982] self-replicating human-inhabited O'Neill space colonies;[983,984] and other speculations[985,986] including interstellar exploration[987] and communication (Section 3.11). Friedman[988] reported in 1996 that the board of directors of SSI had approved "Quest for Self-Replicating Systems" as a worthwhile project, but through 2003[573,989] still had not yet found any specific research proposals that met the criteria for financial support.

In 1996, Raj Reddy[990] at Carnegie Mellon University said of the field of self-replicating systems in space: "There have been several theoretical studies in this area since the 1950's. The problem is of some practical interest in areas such as space manufacturing. Rather than uplifting a whole factory, is it possible to have a small set of machine tools that can produce, say, 80% of the parts needed for the factory, using locally available raw materials and assemble it in situ? The solution to this problem of manufacturing on Mars involves many different disciplines, including materials and energy technologies. Research problems in AI include knowledge capture for replication, design for manufacturability, and design of systems with self-monitoring, self diagnosis and self-repair capabilities."

3.10 Taylor Santa Claus Machine (1978)

Following Shoulders' original suggestion in the early 1960s of particle beam-based replicating machines (Section 4.7), Theodore B. Taylor's concept of the "Santa Claus Machine" was reported in a popular book on advanced space technology published in 1978 by Nigel Calder.[1041] This is the only known extant source on Taylor's idea.

Calder first quotes Taylor, a well-known nuclear physicist and advocate of arms control and small-scale solar energy production on Earth, as follows: "It's possible to imagine a machine that could scoop up material — rocks from the Moon or rocks from asteroids — process them inside and produce just about any product: washing machines or teacups or automobiles or starships. Once such a machine exists it could gather sunlight and materials that it's sitting on, and produce on call whatever product anybody wants to name, as long as somebody knows how to make it and those instructions can be given to the machine. I think the name Santa Claus Machine for such a device is appropriate." Using his own words, Calder then describes the concept in more detail:

"As visualized by Taylor, the machine will operate automatically, without any immediate involvement of human beings. Its central principle will be the sorting of the raw material into all the individual chemical elements which it contains. That will be done by a giant version of the mass spectrograph — an analytical instrument from the physics laboratory which converts material into a beam of ionized (electrified) atoms traveling in a vacuum (Figure 3.32). It then deflects the beam with a magnetic field. Because lightweight atoms accelerate and swerve more readily than heavy atoms the various elements and isotopes in the beam can be sorted, atom by atom.

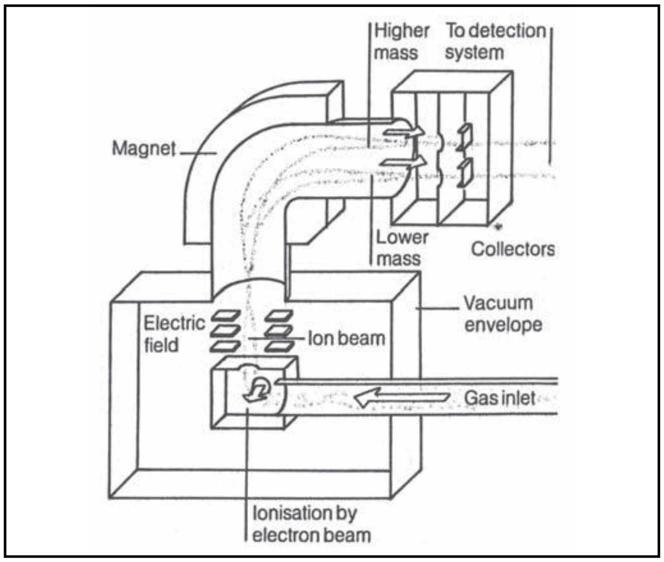


Figure 3.32. Schematic of a laboratory mass spectrometer, the theoretical basis for Taylor's proposed Santa Claus Machine, from Calder.[1041] Santa Claus Machines would take raw materials available in space, for example on the Moon's surface, and separate the materials into their elements, atom by atom, using a mass spectrometer which separates electrically-charged molecules of two different molecular weights. The magnet deflects the lighter molecules more sharply. Scaled up and elaborated greatly, the Santa Claus Machines would then be programmed to use the separated materials in the automatic manufacture of any desired products,[1041] which itself would not be a trivial process.

"In space, nature will provide a ready-made vacuum, allowing the mass spectrograph to be scaled up into a large refining plant.* But it will need big magnets. In Taylor's scheme these may be superconducting electromagnets, working at low temperatures and offering no resistance to the flow of electric current; alternatively, a large machine near the Earth may exploit the weak but extensive magnetic field of the planet itself. At reasonable distances from the Sun, and certainly in the vicinity of the Earth and the Moon, ample power for the Santa Claus Machine will come from solar energy. In the windless vacuum of space one can build large yet flimsy mirrors, like gleaming parachutes. They will focus enough sunshine to vaporize rock. Out among the distant planets, where sunlight becomes feeble, the Santa Claus Machines will run by nuclear power.

"To live up to its name, the Santa Claus Machine must make the stocking-fillers, from the stockpiles of very pure materials created by the mass spectrograph. The materials can be recombined or mixed to make any compound or alloy. According to Taylor, the manufacturing processes will be quite different from what one sees going on in a steel mill or car factory on the Earth. They will take full advantage of the vacuum and weightlessness of space — for example, making parts simply by revaporizing the selected materials and depositing them on moulds. Given a suitable range of automatic tools

---

** The use of electromagnetic enrichment for bulk materials processing was also discussed by Forrester et al[991] in 1978, and was anticipated by similar methods for isotopic enrichment (e.g., the Calutron[992]) that had been in use since the 1940s.[993-995] By 1980, military particle beam line currents of 10^4-10^5 amperes in space-deployed hard-vacuum-environment devices were widely anticipated.[996]*

and process controls in the system, people will simply have to ask for what they want, and tell the machine how to make it.

“Santa Claus Machines in space will supply raw materials and manufactured goods to the Earth. In the beginning, when operations in space are still costly, the products will have to be ones that are very expensive on Earth, in price per pound, and yet command very large markets. In Taylor’s opinion, one may have to talk of markets of hundreds of millions, or even billions, of dollars a year. The most attractive products will be materials like aluminum and titanium which require a lot of energy for their separation. Some of the lunar rocks are far richer in titanium than the titanium ores on Earth. In the long run, practically any material, pure or mixed, will be cheaper and easier to make in space using extraterrestrial sources. For Taylor, the most appealing benefit of large-scale production in space will be its disconnection from the Earth’s biosphere, which will be relieved of pollution. Taylor’s proposal for total separation of the elements means that all of them will come out of the same melting pot, in proportion to the amounts present. Potentially more precious than gold and platinum will be the extraction from extraterrestrial materials of the elements indispensable to life — hydrogen, carbon, nitrogen, oxygen, and so on.

“Apart from serving the Earth’s inhabitants, Santa Claus Machines will have a much wider role in developing the resources of the Solar System. They can orbit the Earth, the Moon or the Sun or latch on to asteroids, the minor planets. Re-adapted to conditions of gravity and wind, they will be able to sit on planets or the moons of planets and gradually transform them. Their manufactured products can include space settlements for human habitation — and even new Santa Claus Machines.”

In recent times, a few researchers[1120] have used the term “Santa Claus Machine” in connection with the field of rapid prototyping using Solid Freeform Fabrication[997-1000] and similar technologies (Section 3.20). The famous “replicator” of the science fiction television and movie series “Star Trek”[1001,1002] also functions as a Santa Claus Machine, having the ability to quickly manufacture food and eating utensils, organic material such as flowers, inorganic materials such as clothing, metallic objects, and even other machines — though never in any episode, to our knowledge, another exact copy of itself.

3.11 Freitas Interstellar Probe Replicator (1979-1980)

In 1963, Bracewell[1003,1004] first suggested using material space probes for interstellar exploration and communication instead of the radio signal approach of traditional SETI (Search for Extraterrestrial Intelligence). In 1974, Arbib[1005] became the first researcher to suggest in the scientific literature* using self-replicating probes** for this purpose: “Developments in artificial intelligence raise the question of the extent to which our eventual interstellar communication will be directly with living creatures, and the extent to which it will be with man-machine symbioses or even with a purely machine intelligence alone. In any case, much of the discussion of interstellar communication posits radio communication as the basic medium. However, we might well imagine trying to design a self-reproducing machine that carries out its own synthesis starting from the interstellar gas. These machines could then reproduce every time they travel a constant distance out from the home planet to yield a sphere moving out from the home planet with a constant density of these self-reproducing machines....What if they start to mutate?...”

Following similar informal speculations by Calder[1041] in 1978 and by Boyce[1043] and Davies*** in 1979, in 1979-1980 Freitas[1014] performed the first quantitative technical engineering analysis of a complete self-replicating interstellar probe, with special attention to materials, structural, and functional closure issues. The possibility of nanotechnology was ignored. The idea of self-replicating interstellar probes was later adopted and widely promoted in 1981 by Tipler[1015,1044] (a physicist often erroneously credited with originating the idea)**** who inadvertently did not mention the earlier work, an omission which he recognized and corrected 13 years later (see Tipler[2885] at pp. 44 (note 36), 350, and 380). Other writers[1016-1018] continue to discuss this idea.

In Freitas’ paper, a nonreplicating Project Daedalus[1022] interstellar flyby space probe (Figure 3.33), with its engineering plans modified to include all subsystems necessary for self-replication, was inventoried for its mass requirements, including 86 distinct device structures. This inventory was then converted to specific mass requirements of 84 chemical elements, conservatively assuming a machine composition distribution similar to the materials consumption of the entire U.S. manufacturing system during 1972-1976,

---

* _It is unknown whether Arbib was inspired by even earlier speculations on spacegoing machine replicating systems by science fiction writers, e.g., the 1967_ Berserker _novel by Fred Saberhagen[671] or Van Vogt’s 1950 novelette trilogy_ Voyage of the Space Beagle[662] _which features self-replicating manufacturing plants that eventually fill a galaxy. Physicist Michio Kaku[1045] claims that Paul Davies “_raised the possibility of a ‘von Neumann probe’ resting on our own moon, left over from a previous visitation in our system aeons ago. If this sounds a bit familiar, that’s because it was the basis of the [1968 science fiction] film, _2001._[2894] Originally, Stanley Kubrick began the film with a series of scientists explaining how probes like these would be the most efficient method of exploring outer space. Unfortunately, at the last minute, Kubrick cut the opening segment from his film, and these monoliths became almost mystical entities._” However, a careful inspection of the text of the screenplay-derived novel_ 2001[2894] _reveals no mention of self-replicating machines, nor does the movie hint at this capability. The first of Clarke’s sequels to_ 2001, _titled_ 2010,[693] _written in 1982, makes it clear for the first time that the black monoliths are now self-replicating entities, but Clarke’s original 1951 short story from which_ 2001 _was derived, called “The Sentinel”,[1006] explicitly describes the found artificial lunar artifact (originally a pyramid, not a rectangular prism) as a lone non-replicating object having been left by extraterrestrial visitors in Earth’s distant past, and not as an interstellar-traveling self-replicating machine._

** _These probes are sometimes called “von Neumann probes”[1043-1045] or “von Neumann machines”,[1007-1009] which generates confusion because the terms “von Neumann machine” and “von Neumann architecture” have, since the mid-1940s, properly referred to the serial-processed stored-program digital computer,[1010,3069] a device which von Neumann personally described[1011] in detail and later helped build (Section 2.1), and thus is (arguably) properly attributable to his name. However, there is no evidence that von Neumann ever described a self-replicating machine in the context of interstellar exploration or interstellar communication and so it seems technically incorrect to name this concept after him. As already noted, Arbib[1005] apparently was the first scientist to propose self-replicating interstellar probes in the technical literature; perhaps “Arbib machines” could be suggested as a more appropriate nontechnical term for this concept, though it is unknown whether Arbib himself was inspired by earlier discussions of the same concept in the science fiction literature.[671] However, the authors (Freitas and Merkle) prefer the simpler technical term “self-replicating probes” since these words are most directly descriptive of the technology involved, do not generate confusion with a previously-coined term currently actively employed in a closely allied technical field, and do not improperly attribute a concept to a person who neither originated nor proposed it. Similarly, personalizing all concepts of nanorobots as “Feynman machines”[1012,1013] or all self-replicating machines of all possible designs as “von Neumann machines”[1013] seems only to opacify and confuse, not enlighten, the discussion._

*** _Writing in 1999,[1019] physicist Paul Davies notes: “Twenty years ago I suggested[1020] in a flight of fancy that an advanced alien civilization might be able to manufacture hybrid machine-organisms that could grow from seeds sent to a suitable host planet. They would develop ‘eyes’, ‘ears’ and other sensors, and even sprout a radio antenna to send back the data, using local resources and energy supplies.”_

**** _Tipler’s most useful contribution to this discussion was his argument[1044] that if advanced extraterrestrial civilizations exist, then they must be capable of building self-replicating probes, and the speed of such replication on geological timescales would make these devices ubiquitous throughout the galaxy in our current epoch; our failure to observe these probes thus serves as evidence that extraterrestrial civilizations do not exist. Sagan and Newman[1021] subsequently published a rebuttal to this argument._

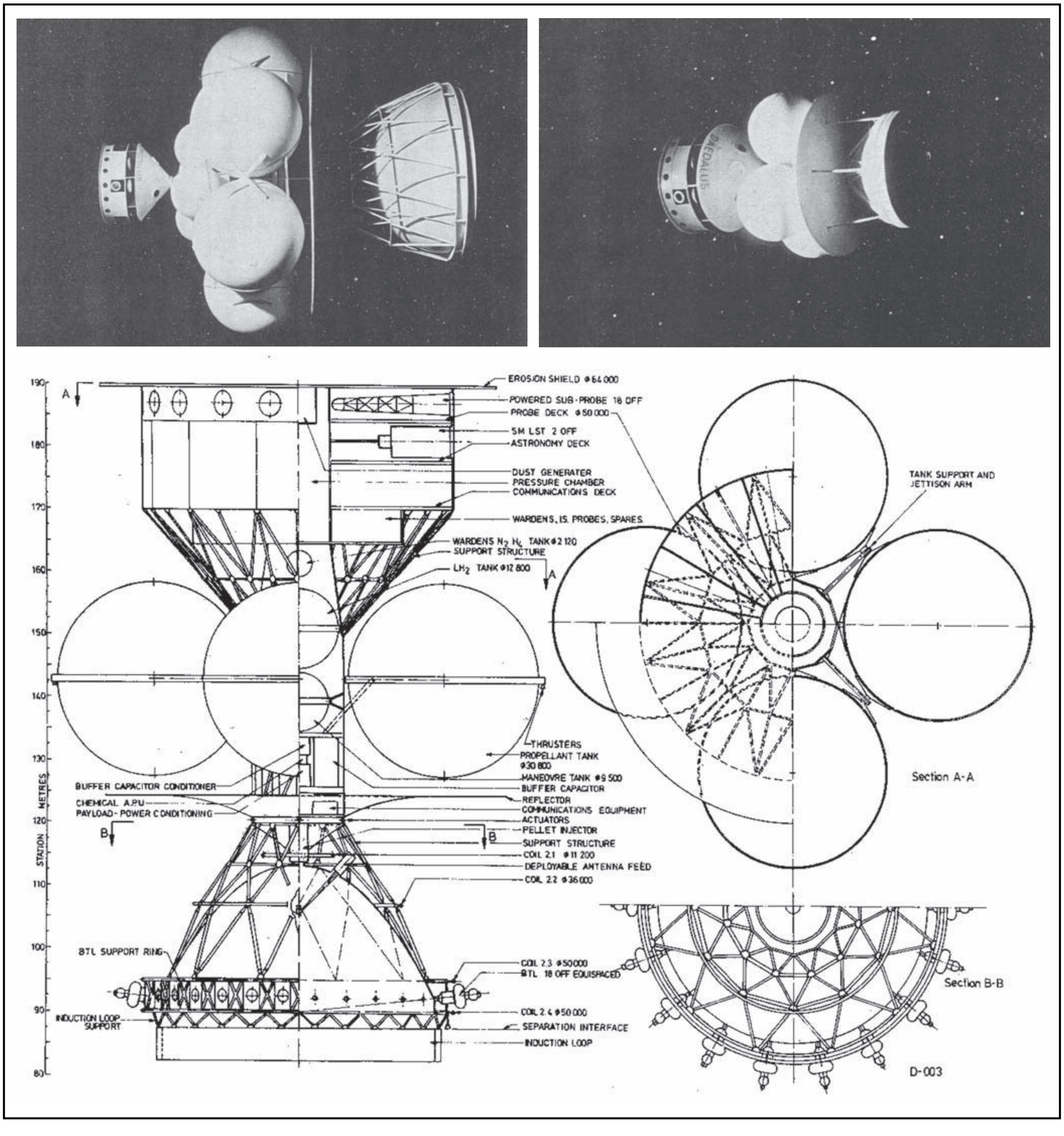


Figure 3.33. Project Daedalus[1022] interstellar flyby probe, modified to carry a self-replicating seed payload.[1014] (courtesy of British Interplanetary Society)

with special adjustments made for certain elements used in industrial processes not relevant to an interstellar probe (e.g., carbon black in tires and dyes, gypsum in construction, silver in coinage), and for other specialty materials preferentially employed in aerospace, electronics, or optical applications. The required element-by-element inventory was then compared to the estimated elemental abundances in a jovian planetary atmosphere or jovian moon materials resource in order to scale the onboard chemical extraction system. The performance characteristics of the extraction system were extrapolated from the known parameters of contemporary ore-processing technologies (and additionally assuming a factor of ten improvement in these parameters) — thus providing the first published worked example of replicating systems materials closure engineering (Section 5.6).

In addition to the fuel and propulsion systems employed in the original Daedalus design study, Freitas' proposed "seed" payload unit (carried aboard each self-replicating interstellar probe) required more than a dozen specified major subsystems to allow self-replication of the entire probe. These subsystems included aerostats for jovian atmospheric mining, surface mining robots, chemical processors, metallurgical processors, a central computer with six redundant data caches (for reliably storing the self-description), fabricator robots, assembly robots, warehouse robots, factory floor crawlers, fuel tankers, repair wardens, inspection robots called verifiers, and power plants. The replicating seed unit was to have a mass of 443 tons, an initial power consumption of 412 MW, and a doubling time of 53.7 years. The final replicated probe had a dry mass of 107,000 tons (roughly the mass of a modern seagoing petroleum supertanker) and was to carry ~10 megatons of He^3/D fusion fuel. The basic replicative strategy[1089] was to (a) use the probe to deliver the seed to a distant site, (b) use the seed to build more of itself, growing itself into a large factory, (c) build more probes (each containing a single seed) using the large factory, and finally (d) launch the new probes to the next distant sites.

3.12 Bradley Self-Replicating Teleoperated Machine Shop (1980)

William E. Bradley studied concepts for building in space in the 1960s when he was associated with the Institute of Defense Analysis, during which time he coined the word telefactor (a slaved machine operated by remote control; or, more commonly today, teleoperation or telepresence). He later became an emeritus member of the board of directors of Telefactor, a company formed in 1972. In 1980, while consulting at NASA Headquarters, Bradley became interested in von Neumann's assertion[3] that "it is in principle possible to set up a machine shop which can make a copy of any machine, given enough time and raw materials." Bradley decided to personally investigate the question of whether a machine shop (Figure 3.34), if properly utilized by knowledgeable human operators and supplied with adequate raw materials, could completely replicate itself.* Bradley concluded that the answer was yes (indeed, building a number of "homebrew" shop machines such as an entire lathe,[1023-1025] drill press[1023] and milling machine[1023] from simpler tools has been demonstrated**). The following material is largely excerpted from Bradley's report.[1026]

The town of Muncy is located in a somewhat remote part of central Pennsylvania. It is remarkable because of a nearly self-sufficient machine manufacturing capability in the Sprout-Waldron Company (now a division of another corporation, and therefore subject to change without notice). This company has manufactured agricultural and food-processing equipment as well as heavy machinery for the paper industry, especially pulp grinders. I became acquainted with them while searching for machines able to produce dense pellets for use as solid fuel from agricultural cellulosic wastes. In the course of my visit, I was shown an excellent machine shop, a foundry, a woodworking shop, and a factory assembly space in which their machines were put together, painted and tested. They also had complete drafting and design engineering facilities. Of special interest was their toolmaking and repair shop, with which all of the milling machines, lathes, jig borers, punch presses, and so forth were kept in fine working order.

This complex, with the possible exception of the foundry, seemed to be a system which, with human assistance, could duplicate itself. In retrospect, it seems worthwhile to explore the possibility that the human operators might be replaced by general purpose automata, manufactured almost completely by the complex itself. The result would then be a major component of a self-replicating system. To complete the system would require manufacture of a prime power source which could be expanded as the complex grows, manufacture of a shelter system (sheds with roofs, walls, windows, and doors) similarly expandable, and possibly a casting and/or forging subsystem, and electronic and computer components of the automata. The foundry with its requirement for refractory furnace linings and high temperatures is a special problem and in some versions of the system may be bypassed.

Figure 3.34. A modern machine shop, in the hands of competent human operators, can replicate most of its own components. (courtesy of Zyvex Corp.)

Present-day machine shops. Each machine in a machine shop has a functional domain or "scope," assuming unlimited operator attention and guidance. Thus, a lathe (with no attachments) is able to produce objects with cylindrical symmetry having axial length and maximum diameter determined by the "bed length" and the "swing" of the machine. It can also make threads (helical structures), and, to a limited extent, can also make straight-line cuts or grooves which are more properly the work of a milling machine. Lathes[1023-1025] can drill holes most readily on the axis of a workpiece of cylindrical symmetry and can achieve a high degree of accuracy of concentricity for this one type of drilling. Most drilling, however, is best accomplished on a jig borer.

The second major machine type in a shop is some form of drill press, or, better, a jig borer. The workpiece is held firmly in an accurately translatable and rotatable fixture, remaining stationary while holes are drilled by a drill or boring tool held in a chuck rotating about the principal axis of the machine. Such a device can produce clusters of accurately located holes with parallel axes.

The third important shop component is the milling machine. The workpiece is clamped firmly to an accurately controlled table. The workpiece moves continuously, slowly, during operations while the rotating milling cutter shaves or saws the surface being worked. The milling machine is usually used to make rectilinear cuts to form accurately related plane surfaces or grooves.

** Von Neumann also observed[1027] that a machine tool that just stamps out parts is an example of a fabricator that is more complex than that which it fabricates. Such a machine tool is "an organization which synthesizes something ... necessarily more complicated...than the organization it synthesizes," so that "complication, or [re]productive potentiality in an organization, is degenerative." In 1970, Nemes[1046] discussed artificial self-replicating machines and described how to construct "an automatic lathe able to reproduce itself," a simple concept said to have been developed even before von Neumann's work on machine replication. Custom machined parts can now be ordered online.[752]*

*** Evidently Doug Goncz[1028] "constructed a self-reproducing machine tool and sold it for $300 in 1997. The machine incorporated its own reproduction template, a drill jig made from 3/8 cold rolled steel." An image of this device was still available online in 2003.[1029]*

Finally, a well-equipped machine shop usually also includes a power hacksaw, a powerful press with forming dies for forming sheet metal and for punching holes with "punch and die" sets, a bending brake, tool grinders, and possibly a surface grinder to be used like a milling machine to produce flat surfaces.

Self-replicating shop and general purpose machines. Each machine or subsystem of such a shop can be separated into parts from which it can be reassembled. Each machine therefore has a "parts list," and each part either can or cannot be fabricated by the set of machines and subsystems comprising the shop. The criterion for replication thus may be stated as follows:

If all parts of all machines and subsystems [including all necessary "scaffold" devices] can be fabricated within the shop, then if properly operated the entire shop can be replicated.

"Proper operation" in this context includes supplying raw materials, energy, and manipulatory instructions or actions necessary to carry out the large number of machine operations, parts storage, and parts assembly required. Human labor is now used for these functions, or to marshal the necessary raw materials and energy.

It is not necessary that the shop be able to produce anything except a replica of itself which is in turn capable of producing another. Therefore, some simplifications appear possible, such as standardization and limitation of scope where feasible. For example, a general purpose machine can be imagined with a wider cross feed table than a conventional lathe and with a standardized vise and tool holder so that it can be used for milling. All three dimensions of translation and one axis of rotation could be provided on the table. The head stock could be arranged to hold workpieces, milling cutters or drills. Hardened tools for the necessary cutting operations could be fabricated by the machine from carbon steel in the annealed condition, then tempered, drawn, and sharpened by a separate simpler machine including a small furnace and a tool grinding wheel equipped with tool-holder and feeds. By careful standardization of parts, tools, and fixtures, it is conceivable that such a "one-machine shop" could succeed in reproducing itself.

Factons. After a shop had been tested with human operators and proven capable of self-replication, it would be possible to explore the replacement of the human operators by mobile computer-controlled manipulators, or "factons." Hopefully, all of the "numerical control" features could be contained in these general-purpose programmable devices which could handle the machines like a human operator. The factons would transfer work from operation to operation, adjust the machine, perform each operation, then transfer the work to a parts storage array. Finally, the parts would be assembled by the factons and the entire shop set up in a selected location and floor plan. The facton itself has a parts list, most designed to be manufacturable by the shop. Here it is practically inevitable that computer chips plus enormous memories will be needed which would fall outside the scope of the shop thus far envisioned. In other words most, but not all, of facton components could be fabricated by factons in the shop. Still, given these extra components provided as feedstock from outside, the factons could probably fully assemble themselves. The shop itself would require some exogenous elements, as noted above: prime power, shaft power transmission such as belting or electric motors, abrasives, furnace heating arrangements for tool heat treatment, and raw material such as basic feedstock including steel rods, strips, and plates are among the most obvious.

Using the same facton design, it should be possible to implement extensions of the shop, including an optical shop, a pneumatic and/or hydraulic equipment manufacturing shop, and ultimately even an integrated circuit shop. Note, however, that only the original shop with its factons and their programs would have to possess the capability for self-replication. Computer components, probably provided from outside the system, might be furnished in an unprogrammed condition. Thus, factons would program the tapes, discs, or read-only memories by replication (and verification) of their existing programs.

Program extension beyond self-replication. The "scope" of a self-replicating shop is much larger than is required for self-replication. Apparently the ability to replicate utilizes only a vanishingly small fraction of total capabilities (to produce various sizes and shapes of parts and to assemble them into machines and structures). The essential characteristic for self-replication is that the scope must be adequate to produce every part of every machine in the shop by means of a feasible program. This "closure condition" (Section 5.6) can be satisfied using only a small part of the shop's full capabilities.

A generic self-replicating machine shop can therefore, by means of a simple addition to its program, manufacture other machines and structures and, by means of them, interact with its environment. For example, it can construct and operate foraging systems to procure fuel or materials, waste disposal systems, or transporters to carry replica shops to other locations. Obviously, self-replication of such an extended system requires replication of the program-memory. This memory can be partitioned into two parts: (1) the self-replication process memory, and (2) the external process (manufacturing) memory. The distinction between these two memories is that the first is required to reproduce the basic unit (shop machines plus factons) while the second memory contains the program to produce process equipment not essential to the self-replicating nucleus.

At this point it is clear that the effect of a self-replicating system on its environment may take many forms dependent on the external process program. Using such a program, the scope of the system can be extended by construction of machines and structures capable of producing complex subsystems including mineral processing plants, solar energy power supplies, etc. All of these extended self-replicating systems would embody the same basic nucleus of machines, factons and self-replication programming. They would differ only by addition of the external process program segment peculiar to each type.

Reliability and redundancy. Reliability is a primary concern, especially in the case of self-replicating processes. Two ideas are most important here.

First, the self-replicating program accuracy can be verified by comparison with other replicas of the same program. If a discrepancy is found between two self-replicating programs, a third or fourth replica can be consulted and the error pinpointed and corrected. The test of correctness is the ability to self-replicate.

Second, machines tend to wear, and ultimately to fail, from normal use. On the other hand, if the system can replicate itself it can make spare parts and install them itself. [Authors' note: this is not a logical necessity, since the shop can in theory produce multiple copies before any part needs to be replaced, and then simply shut down] A special program segment, the "maintenance program," should be devised to check machine wear and perform repairs as needed. This segment would be part of the self-replication program, although another somewhat similar maintenance program should probably be used to care for machines and structures of the external process. This external maintenance program would be specialized for each extended system and is properly part of the second memory. [Authors' note: high fecundity can to some degree compensate for a lack of reliability.]

3.13 NASA Summer Study on Self-Replicating Systems (1980-1982)

By the late 1970s the idea of self-replicating robots had been suggested in various popular writings,[1030-1043] and was beginning to be mentioned, however fleetingly, in more technical publications[1046-1048] — although, as noted by Heer,[1049] the concept had "acid-tongued opponents as well as supporters."* Recognizing the tremendous potential for advanced automation in future space mission planning and development, and suspecting that NASA might not be utilizing fully the most recent results in modern computer science and robotics research, in 1977 Stanley Sadin at NASA Headquarters requested Ewald Heer at the Jet Propulsion Laboratory (JPL) to organize the NASA Study Group on Machine Intelligence and Robotics, chaired by the noted astronomer Carl Sagan. The Sagan Study Group was composed of many leading researchers from almost all major centers in the fields of artificial intelligence, computer science, and autonomous systems in the United States. It included NASA personnel, scientists who worked on previous NASA missions, and experts in computer science who had little or no prior contact with NASA.

The Sagan Study Group met as a full working group or as subcommittees between June 1977 and December 1978, devoting some 2500 man-hours to an examination of the influence of current machine intelligence and robotics research on the full range of space agency activities and recommending ways that these subjects could assist NASA in future missions.[1050] The eye-opening conclusions of the Sagan Group were that NASA was 5-15 years behind the leading edge in computer science and technology, that (unlike its pioneering work in other areas of science and technology) NASA's use of computer science had been conservative and unimaginative, that the overall importance of machine intelligence and robotics for NASA had not been widely appreciated within the agency, and that the advances and developments in machine intelligence and robotics needed to make future space missions economical and feasible would not happen without a major long-term commitment and centralized, coordinated support.

Upon learning of these conclusions, the NASA Advisory Council (NAC) convened a New Directions Workshop at Woods Hole in June 1979. The NAC, a senior group of scientists, engineers, sociologists, economists, and authors chaired by William Nierenberg (Director, Scripps Institute of Oceanography) had become concerned that people in the space program "might have lost some of their creative vitality and prophetic vision of the future".** [1051] Before setting off for Woods Hole, 30 workshop members assembled at NASA Headquarters for briefings on the agency's current program and long range plans, the projected capabilities of the Space Transportation System (the Space Shuttle), and various interesting concepts that had not yet found their way into formal NASA planning. The Workshop members then divided themselves into eight working groups, one of which, the Telefactors Working Group,[1052] was charged with examining possible future applications of very advanced automation technologies in space mission planning and implementation.

The Telefactors Working Group recognized that the cost of traditional space operations, even if transportation became relatively inexpensive, made many proposed large-scale enterprises so expensive that they were not likely to gain approval in any foreseeable funding environment. Long delays between large investments and significant returns made the financial burden still less attractive. The crux of these difficulties was the apparent need to carry fully manufactured machinery and equipment to generate useful output such as oxygen, water, or solar cells in situ. The Group decided to see if the feasibility of certain large-scale projects could be enhanced by using machines or machine systems that could replicate themselves from energy and material resources already available in space. Such devices might be able to create a rapidly increasing population of identical self-replicating factories, which population could then produce the desired finished machinery or products.

To demonstrate the power of the self-replication technique in large-scale enterprises, the Telefactors Working Group assumed a sample task involving the manufacture of 10^6 tons of solar cells on the Moon for use in solar power satellites. A goal of 500 GW generating capacity — to be produced by entirely self-contained machinery, naturally occurring lunar materials, and sunlight for energy — was established. Starting with an initial investment estimated at $1 billion and having placed a 100-ton payload on the surface of the Moon, a nonreplicating or "linear" system would require 6000 years to make the 10^6 tons of solar cells needed — clearly an impractical project — whereas, a self-replicating or "exponentiating" system would need less than 20 years to produce the same 10^6 tons of cells (Figure 3.35). The theoretical and conceptual framework for self-replicating automata was known to exist, though it had never been translated into actual engineering designs or technological models. In practice, this approach might not require building totally autonomous self-replicating automata, but only a largely automated system of diverse components that could be integrated into a production system able to grow exponentially to reach any desired goal. Such systems for large-scale space use would necessarily come as the end result of a long R&D process in advanced automation, robotics, and machine intelligence, with developments at each incremental stage finding wide use both on Earth and in space in virtually every sphere of technology. The Group recommended,[1052] in part, that NASA should "identify minimum feasible systems of this type and consider the possibility of laboratory demonstrations."

As a result of this workshop, NASA decided in September 1979 to fund a major automation feasibility study to be conducted the following year as one of its annual joint NASA/ASEE Summer Study programs. To help provide the Summer Study with a set of futuris-

---

** In 1996, George Friedman[988] lamented that "while still at JPL, [senior aeronautical engineer] Jim Burke tried repeatedly and unsuccessfully to interest the scientific community at Cal Tech and JPL in establishing a prize for the first autonomous self-replicating system. At meetings I attended with the head of JPL's Automation and Robotics activity and the director of USC's robotics laboratory, I was told that — for the scientific and exploration missions they were addressing — self-replication was too difficult, required too long a research schedule and was not necessary anyway."*

*** To complete the historical record, Robert Frosch[1053] recalls: "The origins of the 1979 Woods Hole Workshop were something of a 'put up job'. Bill Nierenberg and I had discussed the atmosphere at NASA, and thought that very high level encouragement of broader and wilder scientific and technological thinking would be a good thing. We thought the NASA Advisory Council (NAC) would be a good vehicle for doing this, and that direct involvement of the members of the NAC would be good for them and for the Agency. So....we cooked up the summer workshop, using a pattern that had been well established by the National Academies and the National Research Council, and, indeed, used the Academies' facility in Woods Hole. Personally, I also regarded it as a chance to engage in some deeper thought about possible NASA long range directions than I usually had time for. I have a happy nostalgic memory of the workshop, at which I spent most of my time with the Telefactors Working Group. As I recall, that group included Barney Oliver of HP, and, for much of the time, James Michener, and the discussions were lively and interesting. I think the workshop had some useful effect on the agency and its future ideas, but not as much as we had hoped. Certainly, we were never able to give self-replication as much push as I would have liked. Too many other problems got in the way, and then the Administration ended and I turned to other subjects and technologies. I still think that NASA has not really used teleoperation and robotics in the ways it could and should. The space station should be much more advanced in this way than it is. I think self-replication holds great promise, especially for making the economics of exploration of the solar system and the universe possible. However, it will take a new view of what constitutes partnership between people and their technology."*

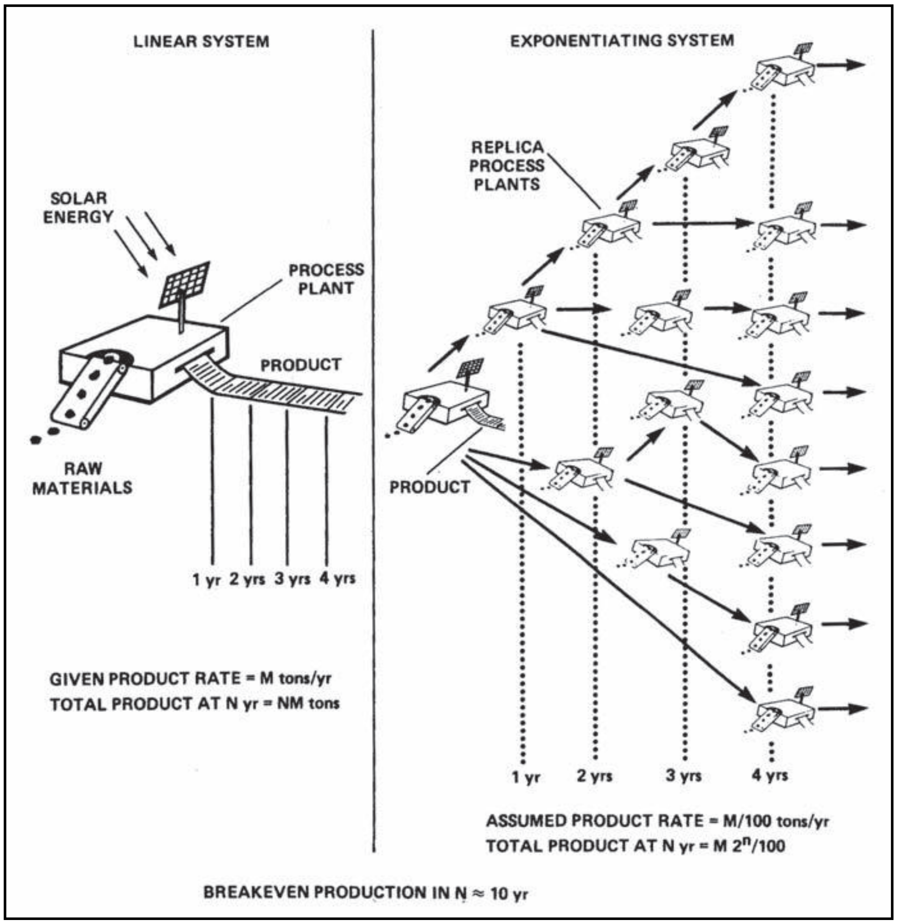

LINEAR SYSTEM
EXPONENTIATING SYSTEM
REPLICA PROCESS PLANTS
SOLAR ENERGY
PROCESS PLANT
PRODUCT
RAW MATERIALS
PRODUCT
1 yr 2 yrs 3 yrs 4 yrs
GIVEN PRODUCT RATE = M tons/yr
TOTAL PRODUCT AT N yr = NM tons
1 yr 2 yrs 3 yrs 4 yrs
ASSUMED PRODUCT RATE = M/100 tons/yr
TOTAL PRODUCT AT N yr = M 2ⁿ/100
BREAKEVEN PRODUCTION IN N ≈ 10 yr

Figure 3.35. Comparison of "linear" and "exponentiating" (self-replicating) manufacturing systems.[2]

tic goals and possibilities, an interactive symposium[1054] was organized by Robert Cannon at the request of NASA Administrator Robert Frosch to take place the week before the opening of the summer session. Accordingly, during the week of 15-22 June 1980, 23 scientists, professors, NASA personnel, and science fiction authors (including Larry Niven and Jerry Pournelle) gathered at Pajaro Dunes near Monterey, California, to consider two specific questions: (1) What goals involving self-replicating telefactors might NASA possibly pursue during the next 25, 50, or 100 years, and (2) what are the critical machine intelligence and robotics technology areas that need to be developed? A large number of highly imaginative missions were discussed, including an automated unmanned (or nearly so) manufacturing facility consisting of perhaps 100 tons of the proper set of machines, tools, and teleoperated mechanisms to permit both production of useful output and replication to make more factories. This mission appears to have generated the most excitement among the symposium participants, in part because it had not yet been extensively studied by NASA (or elsewhere) and the engineering problems were largely unexplored.

Immediately following the conclusion of the brief Pajaro Dunes symposium, the full summer study, entitled "Advanced Automation for Space Missions," was convened on 23 June 1980 at the University of Santa Clara in California, completing its formal work (roughly 10,000 man-hours) on 29 August 1980 (Figure 3.36) at a cost of under $1 million, with the final report, edited by Freitas (also a Study participant), appearing in 1982.[2] During the first two weeks of the 1980 Study, the participants (which included 65 scientists, engineers, professors, and NASA personnel, but no science fiction writers) were introduced to the status of work in artificial intelligence and current NASA programs by a series of lectures given by scientists from SRI International and a number of

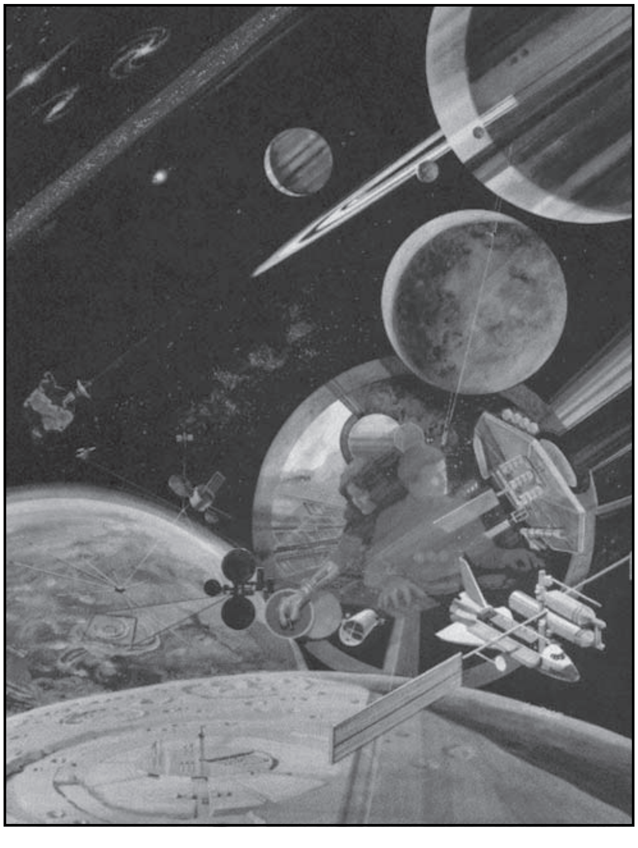


Figure 3.36. 1980 NASA Summer Study theme art, by Rick Guidice (replicating lunar factory at lower left)[2]

NASA program engineers. Study members initially organized into three mission teams to focus on space missions which appeared to have great potential for automation with high relevance to future NASA program goals. One of these three mission teams was titled "nonterrestrial utilization of materials" (NTM) and was to examine the partial automation of a space manufacturing facility (i.e., conventional "bootstrapping"; Section 3.9). The Study leadership informally decided to avoid any direct consideration of the more controversial topic of fully self-replicating systems.

Just months earlier, however, NASA Administrator Robert Frosch had delivered a bold speech[1055] before the influential Commonwealth Club of San Francisco, describing the potential benefits of fully self-replicating systems.* During the third week of the 10-week Summer Study (and once again in Week 5 or 6), Frosch joined the group's deliberations and insisted that some effort should be made to explicitly address the question of fully self-replicating systems. This executive call to action (in Week 3) encouraged four members (Rodger A. Cliff, Robert A. Freitas Jr., Richard A. Laing, and Georg von Tiesenhausen) of the NTM team to break away and establish their own fourth mission team — the Replicating Systems Concepts (RSC) Team — whose work ultimately came to dominate the final report and generated the greatest public interest. (The final administrative report[1056] erroneously recorded that all four teams existed from the start.) Interestingly, three of the four rebels — Freitas,[1014,1089] Laing,[556-563] and von Tiesenhausen** [1088] — had already published their own work in replicating systems theory or design prior to joining the NASA Study; and all four Team members — Cliff,[1057] Freitas,[1075-1081] Laing,[1082] and von Tiesenhausen[1090] — published further work in this area after the conclusion of the Study. Four other NASA Study participants, perhaps emboldened by the RSC Team's efforts, later published work describing or picturing machine self-replication,[1072-1075] and the Team quietly received additional informal intellectual support from many other Study participants. Subsequently the RSC Team's results were widely reported in the popular media[477,1058-1072] and elsewhere,[1083-1087] elicited three post-Study papers by authors associated with NASA,[1090-1092] and directly inspired the writing of at least one science fiction novel, by James P. Hogan,[694] a similar lunar factory study by the Japanese Space Agency,*** [1069] a 1984 University of Notre Dame Master's Thesis,[1093] a legal analysis of nanotechnology replicators,[2965] and several online fan clubs.[1094-1096]

The RSC Team proposed the design and construction of an automated, multiproduct, remotely controlled or autonomous, reprogrammable lunar factory able to construct duplicates (in addition to manufacturing productive output) that would be capable of further replication. Achieving such a factory was to involve a three-stage development approach.

In stage 1, a technology feasibility demonstration of a rudimentary self-replicating system would be performed. The simple replicating system envisioned for stage 1 was a computer connected to one or more manipulators. Under control of the computer, the manipulators would assemble another computer and another set of manipulators from well-defined subassemblies. Examples of these subassemblies are printed circuit cards for the computer and individual joints or limb sections for the manipulators.

In stage 2, the demonstration robot replicator is further refined to produce a less rudimentary system which operates in a less structured environment. Subassemblies would now be assembled from still smaller sub-subassemblies including individual integrated circuit chips, and from discrete electronic and mechanical components such as resistors, motors, bearings, shafts, and gears. Stage 2 would proceed for an extended time as the techniques for assembling each

---

** The relevant portions of NASA Administrator Robert Frosch's September 1979 speech[1055] bear repeating:*

"Given our current technology, and assuming that the initial economic and engineering push to build up to self-sufficiency in the use of extraterrestrial energy and materials would have to be supplied from the Earth, the initial investment requirements by anybody's computation would be very large, in the order of hundreds of billions of dollars. However, there is an intriguing approach to this problem suggested by Freeman Dyson that would detour around the difficulty and provide self sufficient access to the resources of the solar system for a relatively manageable investment. The key to this idea is the construction of a machine which either totally automatically, or with minimal human intervention and guidance, can use solar energy and local materials on the Earth, or on the Moon, or on an asteroid or elsewhere in the solar system to build a replica of itself. Then the machines can construct generation after generation of machines; the total quantity of machines grows exponentially as biological generations grow, rather than linearly, as is the case with an ordinary factory that simply turns out a product.

"This is interesting because of the possibility that such a machine could consist of a solar energy plant plus the manufacturing capability to build another like itself including the solar energy plant. Thus the proliferation of machines would not only entail proliferation of factories having the capability to build factories like themselves, but at the same time would be building a large-scale solar energy plant....It appears possible to start with the investment necessary to put 100 tons of machinery on the Moon and after 20 years of machine reproduction to have an energy plant and manufacturing capability equivalent to the ability to manufacture 20 billion pounds of aluminum a year. I choose aluminum as an example material because it is particularly energy intensive to extract, not because it is necessarily the most interesting material or product. The point is that it appears that one can use machines in a pseudo-biological way to establish a productive machine economy in an extraterrestrial place using extraterrestrial materials and solar energy. This would produce an economic base upon which further exploration of the solar system could be built, and indeed an economic base of tremendous intrinsic potential value for the human race.

"This idea depends entirely on the ability to build a replicating or nearly self-replicating machine. Theorems demonstrating that this is possible have been around for over 15 years, and the idea appeared in fiction long before that. What is different now is that we are very close to understanding how to build such machines. Indeed, I believe that the technology is presently available and that the necessary development could be accomplished in a decade or so. We are now examining such a program both because of its large implications and because of its parochial implications for making it economically possible to continue the great human adventure of exploring our neighborhood, the solar system, and perhaps eventually the universe in which we are embedded."

Five months after these remarks were made, and just four months before the start of the 1980 Summer Study, the usually futurist-friendly Omni Magazine *reported Frosch's comments[1097] with skepticism: "This scenario is a bit of a bombshell, coming as it does from the normally conservative Frosch. It also came as a bit of an embarrassment to some NASA officials, who say in private that the agency doesn't have an in-depth plan for self-replicating robots."*

Just six months later, NASA was given one such plan — but the incoming agency leadership (probably encouraged by institutional resistance) chose not to fund it. Omni Magazine *eventually reported this plan, albeit too late, in a July 1983 full-length article on self-replicating robots written by Freitas.[1080] In a personal letter[1098] to Freitas in June 1983, Robert Frosch lamented: "I continue to be interested in SRS, but know of no one now working seriously on it, nor have I talked on it further. Although I continue to consider it an important subject, I have had to work on other matters."*

*** The late Georg von Tiesenhausen was the assistant director of the Advanced Systems Office at NASA's Marshall Space Flight Center in Huntsville, Alabama. He was formerly a member of the German team of scientists that developed the V2 rocket during World War II, and later came to the U.S. to help launch the American space program. After the NASA summer study was over, von Tiesenhausen[1099] told Freitas that he (GvT) had submitted an official NASA RTOP (Research and Technology Operating Plan) for a new study on replicating systems and methodologies for achieving closure, but evidently nothing ever came of this effort.*

**** Bob Johnstone reported[1069] in 1994 that Japan had developed a similar plan to build research facilities on the Moon. According to one summary: "Japan is considering a plan to construct a lunar station by 2024, built entirely by robots. The proposal includes a first phase, 1999-2005, to land a rover to survey possible sites; a second phase, 2006-2016, to construct pilot plants for the production of food, oxygen and energy; and a third phase, 2017-2023, to build the full-scale facilities, including living quarters for people. The plan includes a permanent staff of six people. International partners would be welcome but are not seen as an essential precondition." Suthakorn[1287] adds: "Research showed that the budget and time requirements could be reduced up to ten times if fully robotic systems were used in this project instead of humans."*

subassembly from sub-subassemblies were developed and implemented one by one.

In stage 3, the previous system would be further expanded in its capabilities, with the manipulators that were used in stages 1 and 2 to assemble robots from ever-smaller parts now used additionally to build the machines which can make the parts. For example, the manipulators would assemble a printed circuit board manufacturing machine or a gear manufacturing machine. This extension of capabilities would ultimately lead to the achievement of a teleoperated, and later a fully autonomous, self-replicating manufacturing facility.*

The RSC Team produced three distinct proposals for kinematic machine replicators, as described below.

3.13.1 NASA Robot Replication Feasibility Demonstration

Directly inspired by von Neumann's original "sea of parts" kinematic machine replicator concept (Section 2.1.2), the NASA robot replicator demonstration[1101] (early draft authored by R. Cliff) begins with a parts depot stocked with enough subassemblies for the production of two robot manipulators and their associated computer systems. For simplicity, all parts are stocked in known positions in designated bins, eliminating much of the need for parts verification during assembly. One complete, operating robot, Robot 1, is initially present and constructs Robot 2 which will, in turn, construct Robot 3 (Figure 3.37), thus passing the "fertility test."

Robot 1 begins its labors by obtaining, one at a time, the subassemblies for the base (which doubles as the electronics card cage assembly) of Robot 2 from the parts depot. Robot 1 assembles the base, computer, and servo controls for Robot 2. Then, one at a time, Robot 1 obtains the subassemblies for the manipulator arms of Robot 2 and constructs the arms of Robot 2 from them. Once Robot 2 has been completely assembled, Robot 1 plugs in the power cord of Robot 2. Finally, Robot 1 obtains a blank diskette (a removable mass memory device for computers) from the parts depot, inserts the diskette into its own computer, copies its software onto the diskette, and then removes the diskette from its own computer. After less than an hour of work, replication is complete when Robot 1 turns on the power to Robot 2, inserts the diskette (which now has a copy of the operating software on it) into Robot 2's computer, and then pushes the start button on the computer. From then on, Robot 2 is autonomous (Figure 3.38).

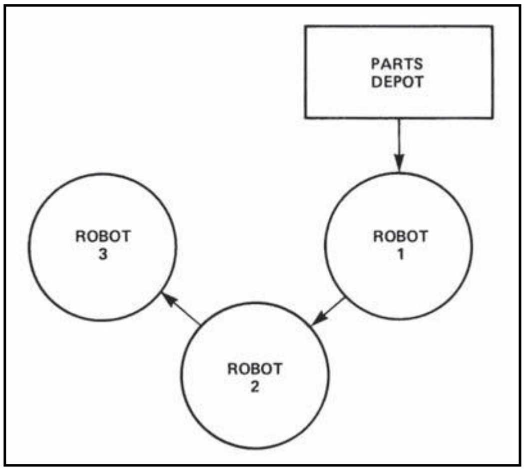


Figure 3.37. Schematic of simple robot self-replication.[2]

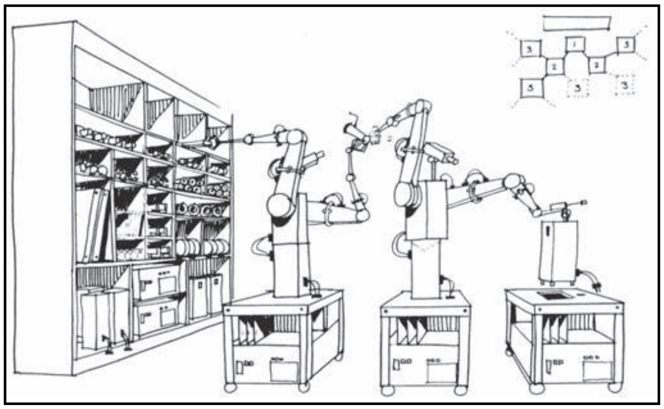


Figure 3.38. Proposed Robot Replication Feasibility Demonstration.[2]

It should be noted that some additional complexity was introduced into the demonstration by explicitly transferring the instructions from one generation of robot to the next by physical movement of a recording medium. This strategy was employed to make it clear that the generations are truly autonomous.

To facilitate multiple demonstrations the robots can be ordered to disassemble one another and return the parts to the parts depot, by following their coded instructions in reverse. Care should be taken to ensure that each of the assembly operations is reversible so that disassembly is possible — bolts should be used in preference to glue, welding, or rivets; mechanical and electrical connections should be engineered to stand up under repeated connection and disconnection; and so forth.

A top-level description[1102] was written of the assembly steps required to produce such a robot manipulator system from about 2 dozen subassemblies, complete with control computer and required electronics support. The NASA demonstration robots were anticipated to be similar to the PUMA industrial assembly robot, which had about 500 distinguishable "parts" with about 50 in the wrist assembly alone.[1102] Replication would include the following sequence: (1) assemble base frame and bolt it to floor; (2) install card cages in frame; (3) install cables between card cages; (4) insert printed circuit cards into card cages; (5) assemble manipulator waist joint support to base frame; (6) install waist joint; (7) install manipulator trunk (vertical member); (8) install shoulder joint; (9) install upper arm; (10) install elbow joint; (11) install forearm; (12) install wrist joint; (13) install end effector; (14) install television camera mast; (15) install television camera; (16) connect television camera to electronics in base; (17) connect manipulator to electronics in base; (18) connect AC power and turn on computer; (19) transfer construction software; and (20) boot up the new computer. Having been replicated as thus detailed, the new robot would then be on its own.

** When some of the work of the RSC Team[1075] was first presented to scientific peers at the Fourth Space Manufacturing Conference in May 1981, Manufacturing Section Chairman Charles Rosen, founder of the Robotics and Automation Division of Stanford Research Institute and chief scientist of the Machine Intelligence Corporation, called it "one of the most important papers in this volume...this growing lunar factory would use as much nonterrestrial material as possible....[and] by replicating that factory as it grows, other factories could be made." Rosen had been involved as a principal automation consultant in the earlier SSI work[2690] on bootstrapping space manufacturing (Section 3.9). During the discussion which followed,[1100] Rosen added: "I am presently attempting to get the National Science Foundation and other groups to put some of their research money into developing self-replicating robots. But it is important to recognize that a complex robot is not essential to make a useful machine. It is possible to design a modular growing robot system, like the early lathes that could produce parts that could make better lathes, which then could produce parts that made better lathes, and so on. But this exercise has not been done. It is a concept that has yet to be explored, although I have very little doubt that if it is useful on Earth it will be explored." Unfortunately, Rosen's initiatives were never funded by NSF, nor, following the exit of Robert Frosch with the change of Presidential Administration in 1981, by NASA.[477]*

Dr. Charles H. Spalding, visited by the RSC Team at the research laboratories of Unimation, Inc. (manufacturer of the PUMA) in Mountain View, California, agreed[1102] that 5 years of adequate funding and manpower support could probably produce a ~1 m^3 robot manipulator system capable of assembling a duplicate of itself from prefabricated parts. On the basis of its many discussions with industry and research community representatives, the RSC Team estimated that it would require about 5 years and \$5-50 million (1980 dollars) to accomplish the proposed robot replication feasibility demonstration.* A substantially similar "robot replication facility" was subsequently described by Dorf and Bishop[1103] in 2001.

3.13.2 Self-Replicating Lunar Factories

Working from von Neumann's clue[2] that "you may break a self-reproductive system into parts whose functioning is necessary for the whole system to be self-reproductive, but which are not themselves self-reproductive," the RSC Team identified two distinct approaches to machine replication. The **first approach** may be called the "unit replication" or organismic model, in which the replicator is an independent unit which employs the surrounding substrate to directly produce an identical copy of itself. Both the original and the copy remain fertile and may replicate again, thus exponentiating their numbers. The **second approach** may be called the "unit growth" or factory model, in which a population of specialist devices, each one individually incapable of self-replication, can collectively fabricate and assemble all necessary components comprising all specialist devices within the system. Hence the factory is capable of expanding its size up to the limits of available resources in an appropriate environment. The factory model is often employed in discussions of "bootstrapping," which is the creation of more productive capacity, from less, using the original capacity. In early systems, control signals could be provided from outside, yielding a purely teleoperated replicator; in more mature systems, control could be increasingly internalized, possibly leading to full control autonomy (Section 5.1.9 (A1)).

Note that either type of machine replicator, in order to be useful, must be capable of manufacturing useful non-self product. The scheduling of lunar factory operational phases (Figure 3.39) was regarded as flexible and subject to optimization for different missions. As Merkle[211] reiterated more eloquently a decade later: "An important point to notice is that self-replication, while important, is not by itself an objective. A device able to make copies of itself but unable to make anything else would not be very valuable. Von Neumann's proposals centered around the combination of a Universal Constructor, which could make anything it was directed to make, and a Universal Computer, which could compute anything it was directed to compute. This combination provides immense value, for it can be re-programmed to make any one of a wide range of things. It is this ability to make almost any structure that is desired, and to do so at low cost, which is of value. The ability of the device to make copies of itself is simply a means to achieve low cost, rather than an end in itself."

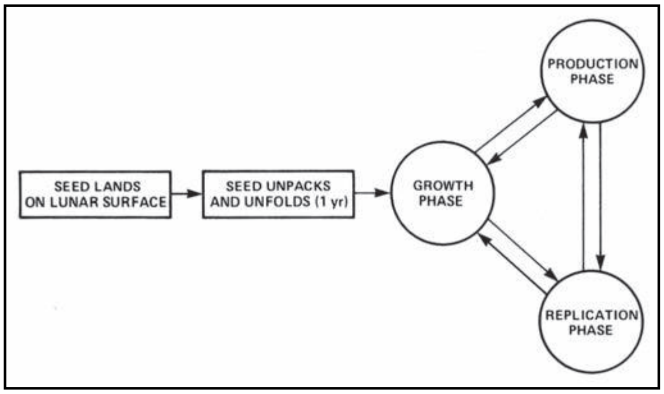


Figure 3.39. Flexible scheduling of self-replicating lunar factory operational phases.[2]

3.13.2.1 Von Tiesenhausen Unit Replication System

The design for unit replication, grounded in earlier work by RSC Team member von Tiesenhausen,[1088] was intended to be a teleoperated or fully autonomous, general-purpose self-replicating factory to be deployed on the surface of planetary bodies or moons. Four major subsystems comprise each replication unit (Figure 3.40). First, a materials processing subsystem acquires raw materials from the environment and prepares industrial feedstock from these substances. Second, a parts production subsystem uses the feedstock to make machines or other parts. At this point, factory output may take two forms: Parts may flow either to the universal constructor subsystem, where they are used to construct a new replication unit (replication), or they may flow to a production facility subsystem to be made into commercially useful products (production). The factory includes a number of other important subsystems, including:

1. **Materials processing and feedstock production**. In this system, raw materials are gathered by strip or deep mining. They are then analyzed, separated, and processed into industrial feedstock components such as sheets, bars, ingots, castings, and so forth, which are laid out and stored in the materials depot.
2. **Materials depot**. The materials depot collects and deposits in proper storage locations the various feedstock categories according to a predetermined plan which ensures that the subsequent fabrication of parts proceeds in the most efficient manner possible. The depot also serves as a buffer during interruptions in normal operations caused by failures in either the materials processing subsystem (depot input) or in the parts production subsystem (at depot output).

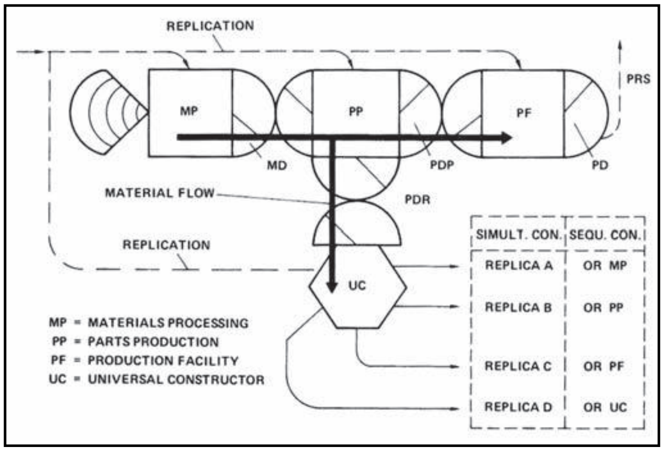


Figure 3.40. Functional schematic of unit replication factory.[2]

** Just 22 years later, a significant portion of the proposed NASA replicating robot demonstration was finally achieved (Sections 3.23 and 3.25.2) using small LEGO®-based devices made from four complex parts in a robotics laboratory in the Department of Mechanical Engineering at Johns Hopkins University.*

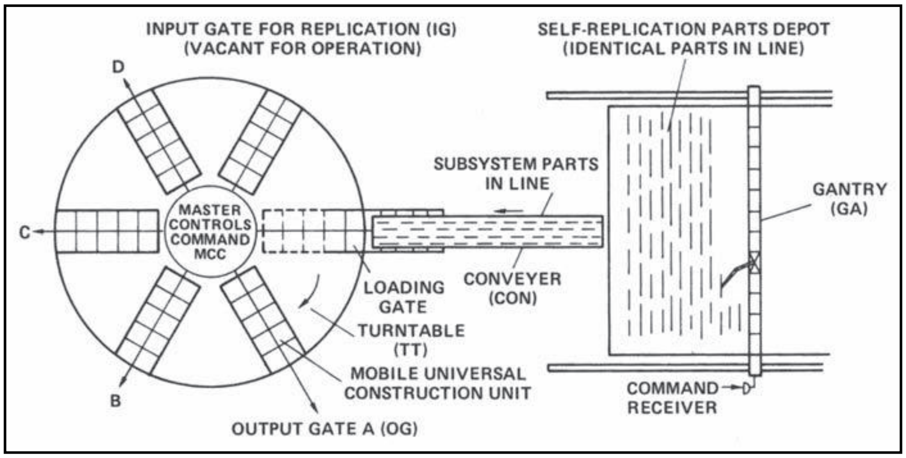


Figure 3.41. Unit replication factory stationary “universal constructor.”[2]

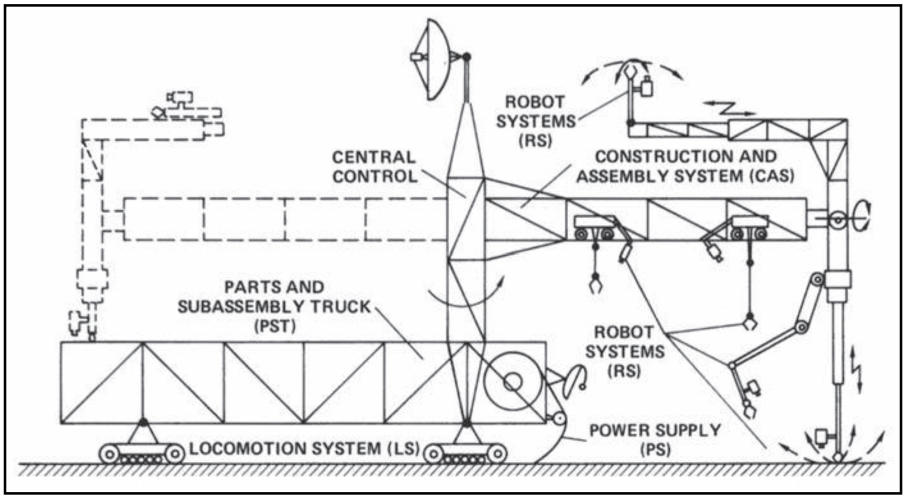


Figure 3.42. Unit replication factory mobile “universal constructor.”[2]

3. **Parts production plant**. The parts production plant selects and transports industrial feedstock from the materials depot into the plant, then fabricates all parts required for factory production or replication activities. Finished parts are stored in the production parts and the replication parts depots, respectively.
4. **Parts depots**. There are two parts depots in the present design, called the production parts depot and the replication parts depot. Parts are stored in the production parts depot exclusively for use in the manufacture of useful products in the production facility. If certain raw materials other than parts and subassemblies are required for production, these materials are simply passed from the materials depot through the parts production plant unchanged. The parts production depot also acts as a buffer during interruptions in normal operations caused by temporary failures in either the parts production plant or the production facility. Parts and subassemblies are stored in the replication parts depot exclusively for use in factory replication activities. Storage is in lots earmarked for specific facility construction sites. The replication parts depot also serves as buffer during interruptions in parts production plant or universal constructor operations.
5. **Production facility**. The production facility manufactures the desired useful products. Parts and subassemblies are picked up at the production parts depot and are transported to the production facility to be assembled into specific useful products. Finished products are then stored in the products depot, but ultimately are collected by the product retrieval system for outshipment.
6. **Universal constructor**. The universal constructor manufactures complete replication units which are exact duplicates of the original system. Each replica can then, in turn, construct more replicas of itself, and so on. The universal constructor retains overall control and command responsibility for its own replication unit as well as its own replicas, until the control and command functions have also been replicated and transferred to the replicas. These functions can be overridden at any time by external means. The universal constructor subsystem consists of two major, separate elements — the stationary universal constructor (Figure 3.41) and the mobile universal constructors (Figure 3.42). This composite subsystem must successfully perform a number of fundamental tasks, including receiving, sorting, loading, and transporting parts and subassemblies; assembling, constructing, installing, integrating, and testing unit replication systems; starting and controlling unit replication operations; and copying and transferring instructions between system components.
7. **Products depot**. The outputs of the production facility are stored in the products depot, ready for retrieval. Major hardware components are neatly stacked for ready access by the product retrieval system. Consumables such as elemental oxygen are stored in reusable containers that are returned empty to the production facility. The products depot also serves as a buffer against variable output and retrieval rates.
8. **Product retrieval system**. The product retrieval system collects the outputs of all replication units in a “factory field” and carries them to an outside distribution point for immediate use or for subsequent outshipment.

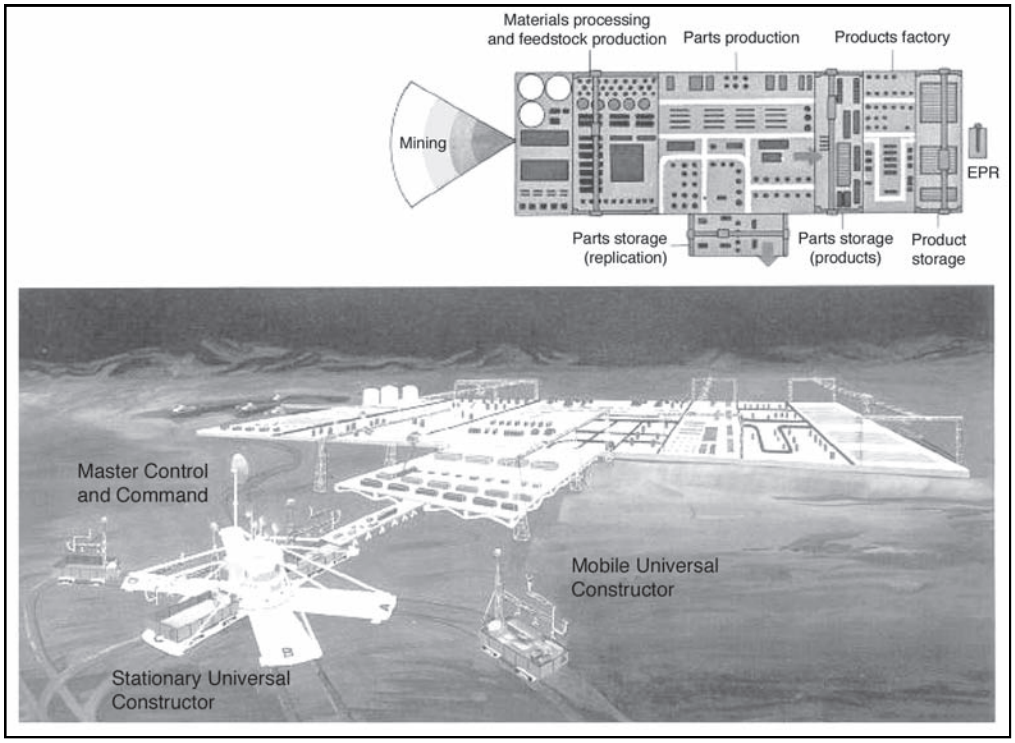

Materials processing and feedstock production
Parts production
Products factory
Mining
EPR
Parts storage (replication)
Parts storage (products)
Product storage
Master Control and Command
Mobile Universal Constructor
Stationary Universal Constructor

Figure 3.43. Unit replication lunar factory.[2]

9. **Command and control systems**. The master control and command system, located within the stationary universal constructor, is programmed to supervise the total factory operation and to communicate both with the peripheral controls of the mobile universal constructors during the self-replication phase and with the replicated stationary universal constructor during the transfer of command and control for the operation of the new replica unit. The master control and command system operates its own replication unit through individual communication links which address the local control and command systems of individual factory elements. In this way the master control and command system supervises the condition and operations of its own system elements, from materials acquisition through end product retrieval.
10. **Energy system**. The power requirements for the present design may be in the gigawatt range. A single energy source (such as a nuclear power plant) would be excessively massive and difficult to replicate, leaving solar energy as the lone viable alternative. Daylight options include: (A) central photovoltaic with a ground cable network, (B) distributed photovoltaic with local distribution system, (C) individual photovoltaic, and (D) satellite power system, with microwave or laser power transmission to central, local, or individual receivers. Nighttime power options include MHD, thermionics, or turbogenerators using fuel generated with excess capacity during daytime. Oxygen plus aluminum, magnesium, or calcium could be used for fuel. A 15% efficient central silicon photovoltaic power station was assumed in the reference design, with an output of tens of gigawatts and a size on the order of tens of square kilometers for an entire factory field. Each replication unit must produce, in addition to its scheduled line of regular products, a part of the photovoltaic energy system equal to the energy needs of its replicas. These are retrieved along with the regular products by the product retrieval system and are assembled on-site to increase energy system capacity according to demand during the self-replication phase.

A single lunar replication unit, erected on the surface of the Moon, might appear as illustrated in Figure 3.43. As a unit replication scheme, the multiplication of replication units proceeds from a single primary system to many hundreds of replica systems. This expansion must be carefully planned to reach the desired factory output capacity without running out of space and materials. Figure 3.44 shows one possible detailed growth plan for the geometry of a factory field. In this plan, each factory constructs just three replicas simultaneously, then abandons replication and goes into full production of useful output. After the three generations depicted, a factory field network 40 units strong is busy manufacturing products for outshipment.

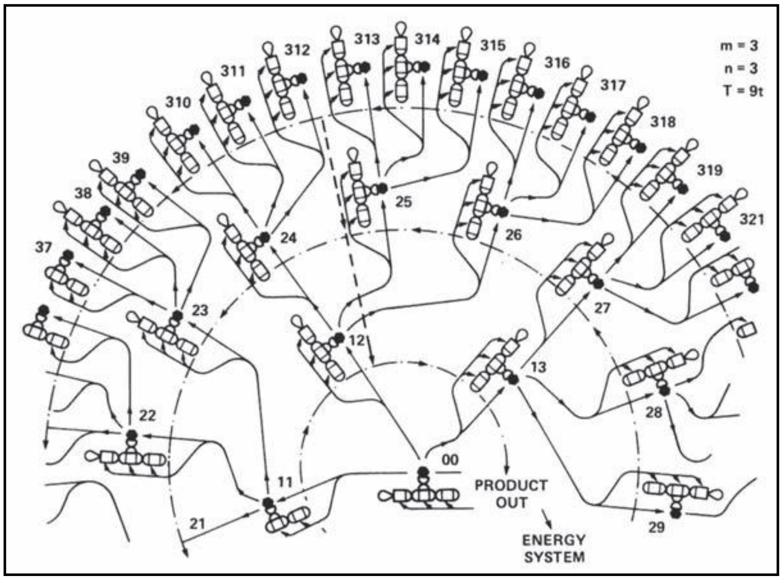


Figure 3.44. Possible growth plan with simultaneous replica construction of a field of lunar factories.[2]

3.13.2.2 Freitas Factory Replication System

The design for unit growth, grounded in earlier work by RSC Team member Freitas,[1014] was intended to be a teleoperated or fully autonomous general-purpose factory which expands to some predetermined mature size starting from a relatively tiny "seed" initially deposited on the lunar surface that unpacks and begins to grow. This seed, once deployed on the Moon, remains circular in shape, thus providing the smallest possible perimeter/surface area ratio and minimizing interior transport distances. Expansion is radially outward with an accelerating radius during the growth phase. The factory platform is divided into two identical halves (Figure 3.45), each composed of three major production subsystems: (1) the chemical processing sector, which accepts raw lunar materials, extracts needed elements, and prepares process chemicals and refractories for factory use; (2) the fabrication sector, which converts these substances into manufactured parts, tools, and electronics components; and (3) the assembly sector, which assembles fabricated parts into complex working machines or useful products of any conceivable design. Each circular growth unit includes eight fundamental subsystems, the first three of which are external to the main factory floor, as follows:

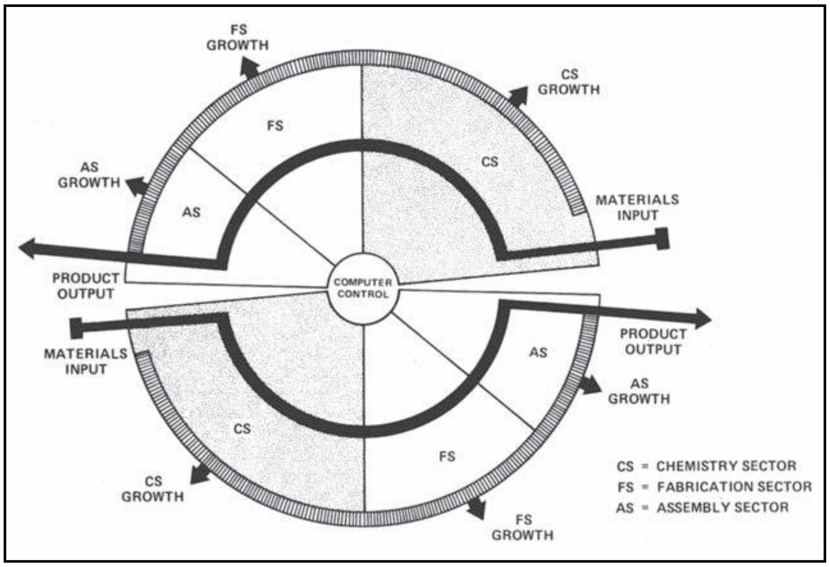


Figure 3.45. Functional schematic of unit growth factory.[2]

1. **Transponder network**. A transponder network operating at gigahertz frequencies assists mobile factory robots in accurately fixing their position relative to the main factory complex while they are away from it. The network is composed of a number of navigation and communication relay stations set up in a well defined regular grid pattern around the initial seed and the growing factory complex. This may be augmented by a lunar GPS.
2. **Paving robots**. In order to secure a firm foundation upon which to erect seed (and later factory) machinery, a platform of adjoining flat cast basalt slabs is required. In the baseline design, a team of five paving robots lays down this foundation in a regular checkerboard pattern, using focused solar energy to melt pregraded lunar soil in situ.
3. **Mining robots**. Factory mining robots perform six distinct functions in normal operation: (1) strip mining, (2) hauling, (3) landfilling, (4) grading, (5) cellar-digging, and (6) towing. Lunar soil is strip-mined in a circular pit surrounding the growing seed and hauled back to the factory for processing, after which the unused slag is returned to the inside edge of the annular pit and used for landfill which may later be paved over to permit additional factory radial expansion. Paving operations require a well graded surface, and cellar digging is necessary so that the central computer may be partially buried a short distance beneath the surface to afford better protection from potentially disabling radiation and particle impacts. Towing is needed for general surface transport and rescue operations to be performed by the mining robots. The robot design selected is a modified front loader with combination roll-back bucket/dozer blade and a capacity for aft attachments including a grading blade, towing platform, and a tow bar.
4. **Chemical processing sectors**. Mining robots deliver raw lunar soil strip-mined at the pit into large input hoppers arranged along the edge of entry corridors leading into the chemical processing sectors in either half of the factory. This material is electrophoretically separated[1104] into pure minerals or workable mixtures of minerals, then processed using the HF acid leach method[1105,1106] and other specialized techniques to recover volatiles, refractories, metals, and nonmetallic elements. Chemical processing operations are shown schematically in Figure 3.46. Useless residue and wastes are collected in large output hoppers for landfill. Buffer storage of materials output is on site.
5. **Fabrication sectors**. The factory fabrication sector is an integrated system for the production of finished aluminum or magnesium parts, wire stock, cast basalt parts, iron or steel parts, refractories, and electronics parts. As shown in the basic operational flowchart for parts fabrication (Figure 3.47), there are three major subsystems: (1) the casting subsystem, consisting of a casting robot to make molds, mixing and alloying furnaces for basalt and metals, and automatic molding machines to manufacture parts to low tolerance using the molds and alloys prepared; (2) the laser machining and finishing subsystem, which performs final cutting and machining of various complex or very-close-tolerance parts; and (3) the electronics fabrication subsystem.[1074]
6. **Assembly sectors**. Finished parts flow into the automated assembly system warehouse, where they are stored and retrieved by warehouse robots as required. This subsystem provides a buffer against system slowdowns or temporary interruptions in service during unforeseen circumstances. The automated assembly subsystem requisitions necessary parts from the warehouse and fits them together to make subassemblies which are inspected for structural and functional integrity. Subassemblies may be returned to the warehouse for storage, or passed to the mobile assembly and repair robots for transport to the factory perimeter, either for internal repairs or to be incorporated into working machines and automated subsystems which themselves may contribute to further growth. The basic operational flowchart for factory parts assembly is shown in Figure 3.48.
7. **Solar canopy**. The solar canopy is a roof of photovoltaic solar cells, suspended on a relatively flimsy support web of wires, crossbeams and columns perhaps 3-4 meters above ground level. The canopy covers the entire factory platform area and expands outward as the rest of the facility grows. The solar canopy and power grid provide all electrical power for factory systems. Canopy components may be stationary or may track solar motions using heliostats if greater efficiency is required.

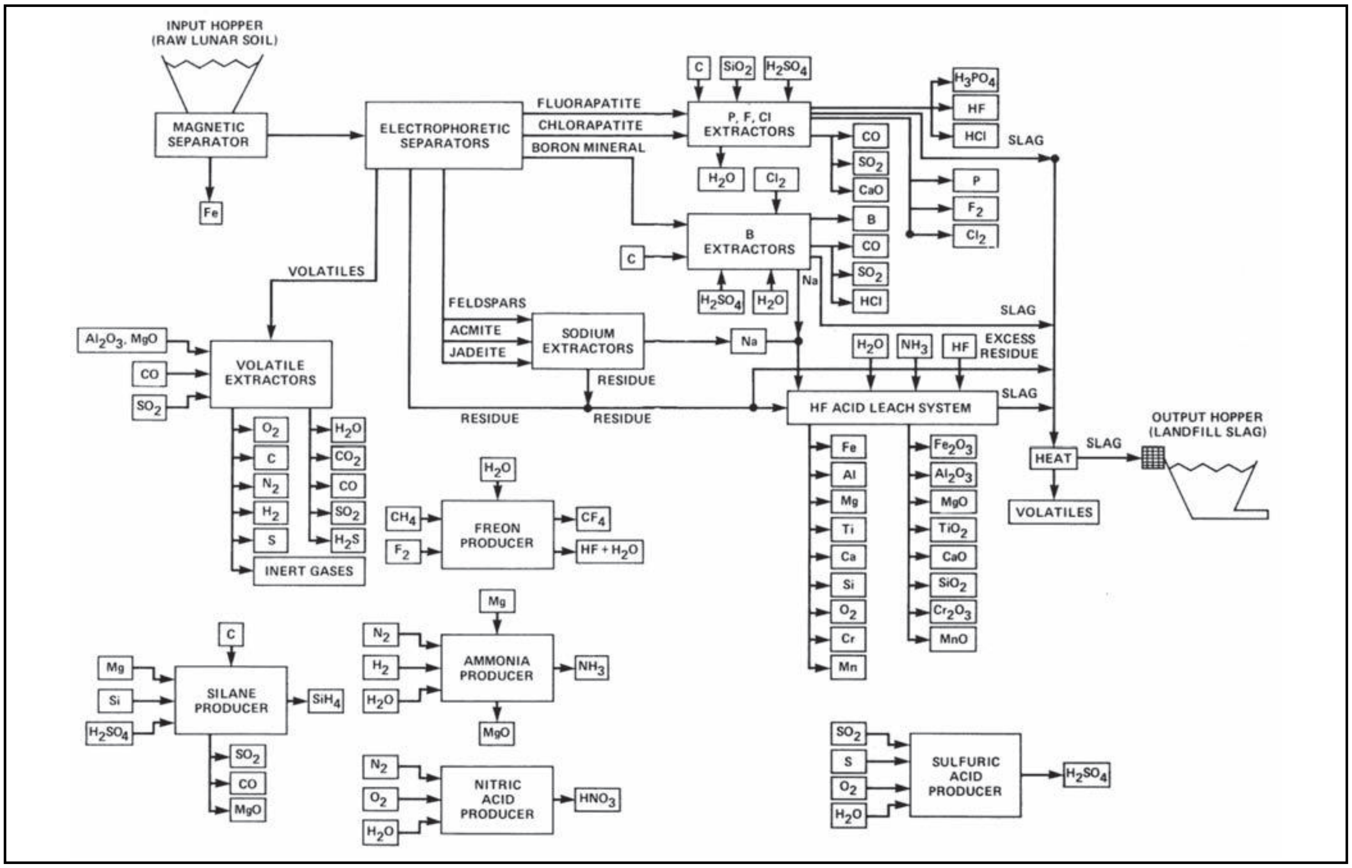


Figure 3.46. Unit growth factory chemical processing sector.[2]

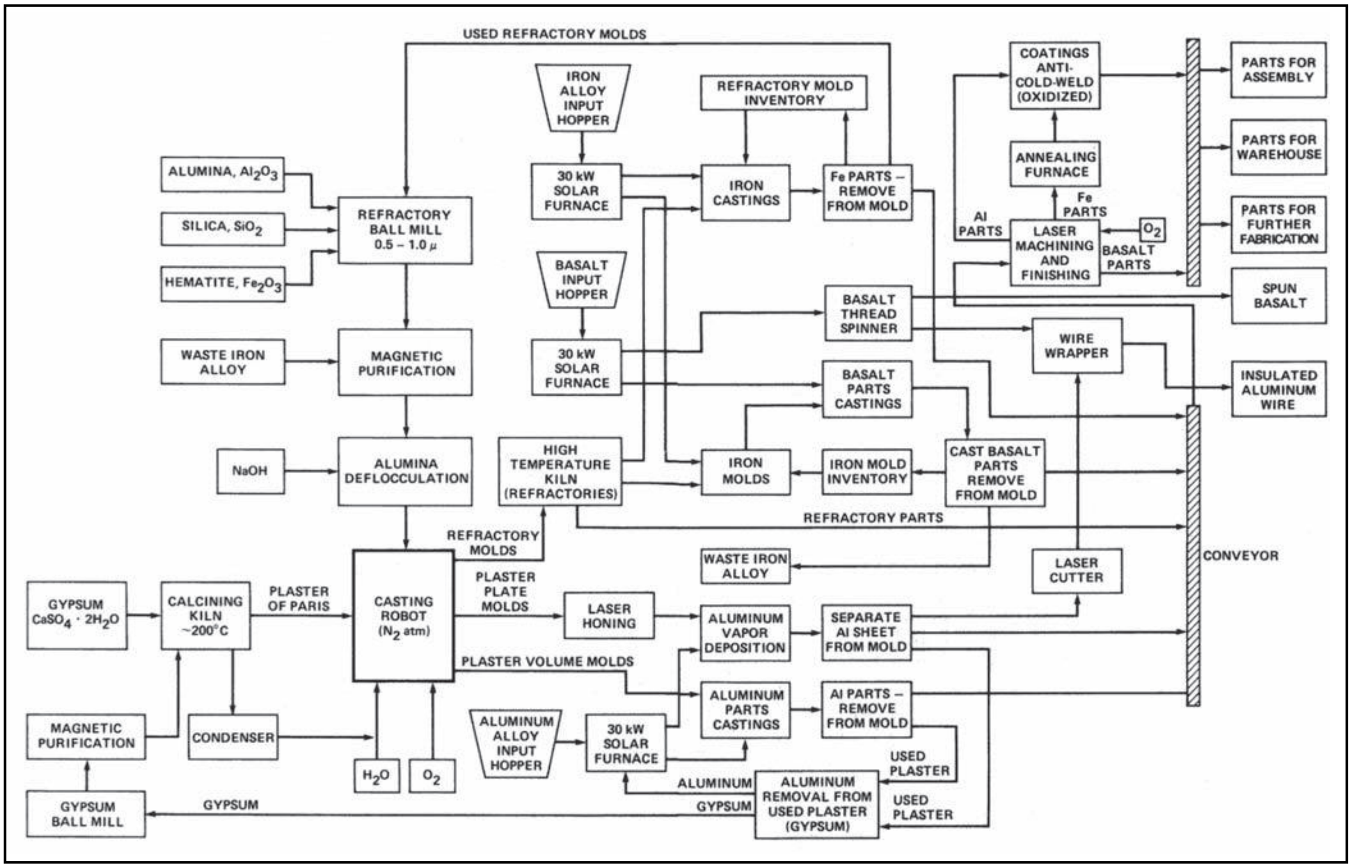


Figure 3.47. Unit growth factory parts fabrication sector.[2]

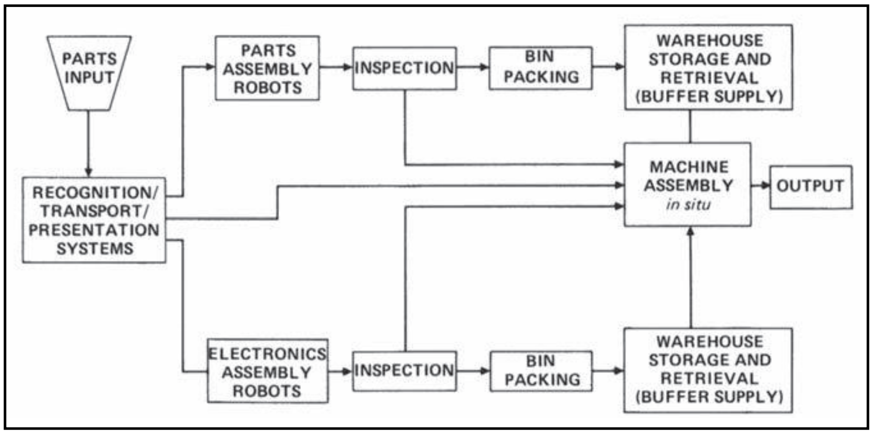

PARTS INPUT
PARTS ASSEMBLY ROBOTS
INSPECTION
BIN PACKING
WAREHOUSE STORAGE AND RETRIEVAL (BUFFER SUPPLY)
RECOGNITION/ TRANSPORT/ PRESENTATION SYSTEMS
MACHINE ASSEMBLY in situ
OUTPUT
ELECTRONICS ASSEMBLY ROBOTS
INSPECTION
BIN PACKING
WAREHOUSE STORAGE AND RETRIEVAL (BUFFER SUPPLY)

Figure 3.48. Unit growth factory assembly sector.[2]

8. **Computer control and communications**. The seed computer must allow the deployment and operation of a highly complex, teleoperated or completely autonomous factory system. The original computer must erect an automated production facility, and must be expandable in order to retain control as the factory grows to its full mature size. The computer control subsystem may coordinate all aspects of production, scheduling, operations, repairs, inspections, maintenance, and reporting, and must stand ready to respond instantly to emergencies and other unexpected events. Computer control is nominally located at the hub of the expanding factory disk, and commands in hierarchical fashion a distributed information processing system with sector computers at each node and sector subsystems at the next hierarchical level of control. In a practical sense, it is quite possible to imagine the lunar factory operating nonautonomously.[1107] For instance, the in situ computer could be used simply as a teleoperation-management system for operations controlled directly by Earth-based workers. Material factory replication would proceed, but much of the information necessary to accomplish this would be supplied from outside — partially anticipating the concept of the "broadcast architecture" in nanotechnology assemblers (Section 4.11.3.3). Other alternatives were to permit the on-site computer to handle mundane tasks and normal functions with humans retaining a higher-level supervisory role, or to allow people to inhabit the machine factory and help it replicate as a manned machine economy.

A seed mass of 100 tons was assumed because: (A) this mass (~4 lunar excursion modules) was considered a credible system mass in terms of foreseeable NASA launch capabilities to the lunar surface; (B) many subsystems appeared to be approaching a nonlinear scaling regime for smaller systems (in this pre-nanotechnology analysis); (C) similar figures had emerged from prior studies of semi-automated[2690] and fully-automated [1014] replicating factory systems; and (D) the figure had appeared in public discussions by former NASA Administrator Frosch[1055] and by others in prior studies.[1051,1052] A replication time of 1 year was assumed for similar reasons, leading to an initial seed power requirement of 1.7 MW and an initial deployed diameter of 120 meters.

A single lunar seed unit, erected on the surface of the Moon, might appear as illustrated in Figure 3.49. In the baseline deployment scenario, the seed factory lands at a predetermined site and the mobile assembly and repair robots are deployed from the master control and command center. They assemble a small interim solar array and the first three transponder network stations, after which the mining and paving robots begin laying the seed platform. Finally, the master control and command center is moved to the middle and the solar canopy is assembled, the entire process taking one year. Thereafter, the factory can: (1) grow itself larger to its optimum limit, (2) replicate further copies of itself for distribution to neighboring locales, or (3) commence manufacturing valuable products or commodities. For example, a factory that had undergone thousand-fold growth after 10 years of self-replication would represent a 2 gigawatt power generating facility.

An important aspect of this design is that unlike previous bootstrapping studies which assumed at most 90-96% materials closure (Section 5.6), the Team's theoretical design goal for the self-replicating lunar factory was 100% materials, parts (both fabrication and assembly), and energy (though not necessarily 100% information) closure. An effort was made to specify all the chemical elements that would be required to build all systems, and then to make sure that all of these elements could be produced in adequate quantities by the chemical processing subsystem. This specifically included on-site chip manufacturing (as discussed in Section 4.4.3 of the NASA report[2] and in Zachary[1074].) Of the original 100-ton seed, the chip-making facility was estimated to have a mass of 7 tons, drawing about 20 kW of power (Freitas and Gilbreath[2] at Appendix 5F, p. 293). 100% materials closure was achieved "by eliminating the need for many...exotic elements in the SRS design... [resulting in] the minimum requirements for qualitative materials closure....This list includes reagents necessary for the production of microelectronic circuitry." (Freitas and Gilbreath[2], pp. 282-283)

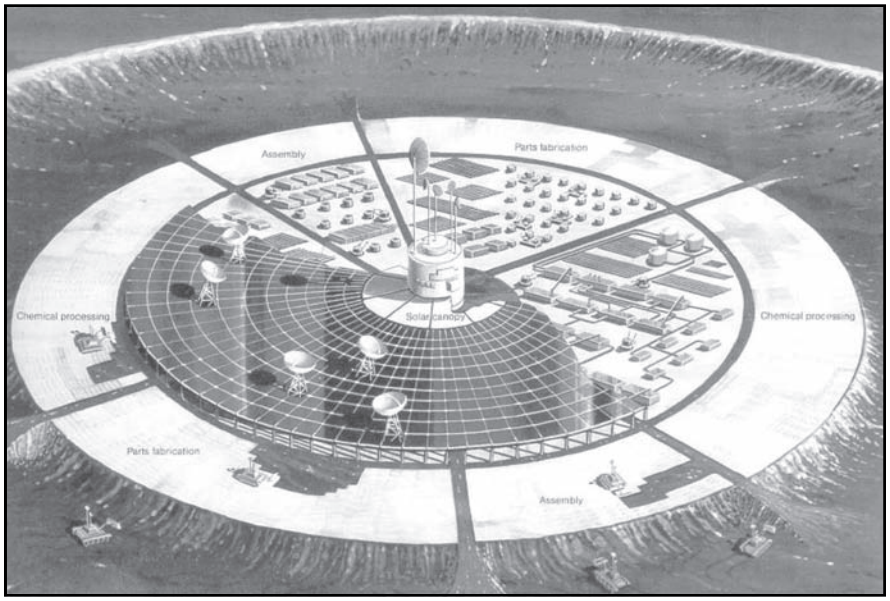


Figure 3.49. Unit growth lunar factory.[2]

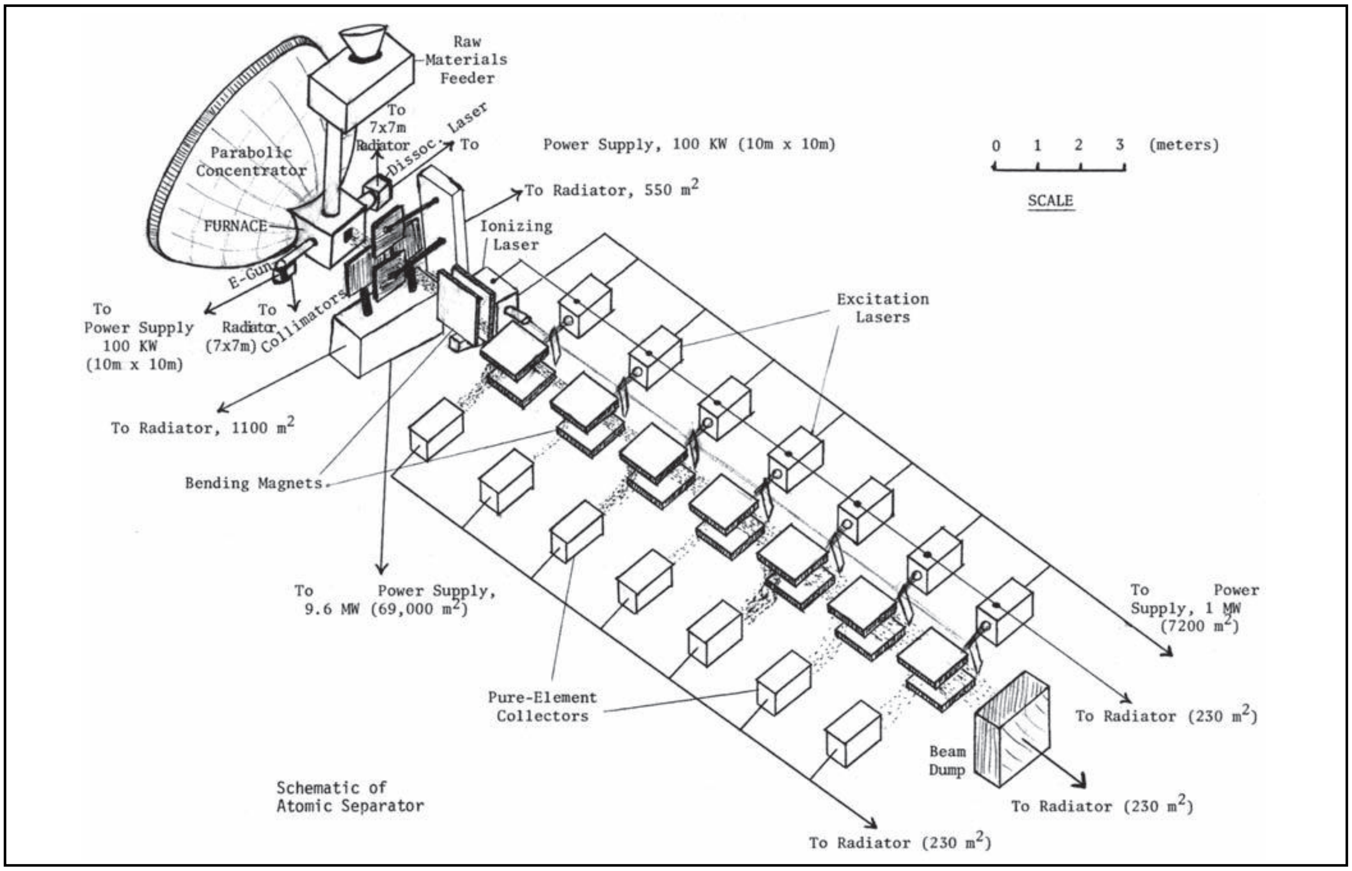


Figure 3.50. Schematic of Freitas atomic separator replicator.[1108]

3.14 Freitas Atomic Separator Replicator (1981)

Following in the tradition of Shoulders (Section 4.7) and Taylor (Section 3.10), in 1981 Freitas[1108] privately circulated an unpublished basic technical analysis of the potential problems and performance characteristics of a space-based solar-powered "atomic separator" replicator using a fully-dissociated materials input beam, laser separation of isotopes, and raster-scan production of parts. This analysis was intended as a simple scaling study, not as a full systems design.

In this scenario, raw lunar or asteroidal material is delivered to a parabolic solar furnace where it is heated to ~5000 K at the focus, irradiated by a pulsed-mode laser and electron gun raising the vapor temperature to ~6 eV, collimated and accelerated through metal plates, then passed through bending magnets which remove ionized species for recycling, leaving a collimated hot neutral atomic beam. This beam enters a linear laser isotope separation[1109] chamber in which a series of magnets and tunable excitation lasers allow atoms of selected pure elements to be picked out of the beam and diverted to collectors, with a beam dump at the far end that collects unused material for reuse or disposal. Collected atoms, thus sorted, can then be employed in a beam-deposition scheme in which pure elemental feedstock is ionized and electrostatically delivered to a workpiece, building up parts and larger systems by a raster-scan type deposition process similar to processes which in later years have become known as stereolithography,[1110-1119] fused deposition modeling (FDM),[933-935] electrodeposition microfabrication (EFAB™),[1122-1124] gas phase solid freeform fabrication (SFF),[1125-1127] and so forth, as briefly reviewed in Section 3.20.

The main device (Figure 3.50) is a cylinder averaging ~5 meters wide and ~20 meters long, not counting 1100 m² of waste heat radiators and 76,400 m² of solar power panels producing 11 MW of power. The estimated net mass throughput of atomically sorted atoms is ~0.00125 kg/sec. Assuming mean system density is ~100 kg/m³ (it is mostly vacuum) and the panels and radiators are 1 cm thick in the complete system deployed in lunar orbit (Figure 3.51), then the atomic separator replicator has a mass of ~120 tons and a net production rate of ~40 tons/year, hence can process its own mass of materials in ~10^8 sec, a ~3 year replication time.

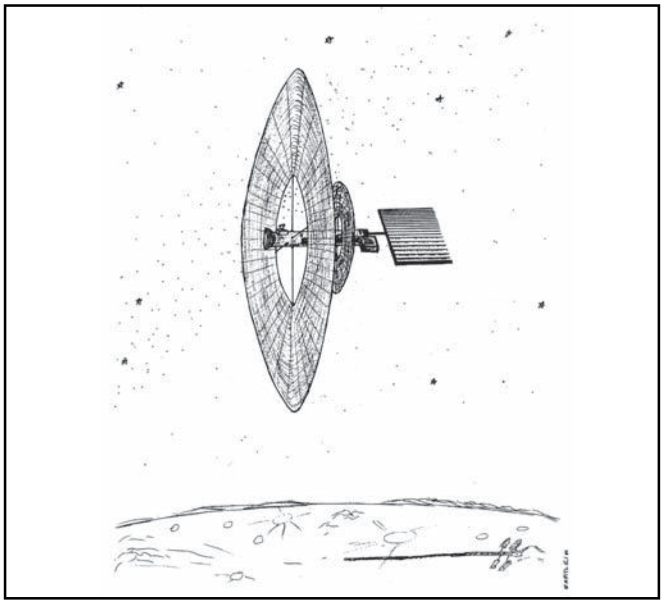


Figure 3.51. Atomic separator with power and radiator systems deployed in lunar orbit (central module drawn 3X actual scale).[1108]

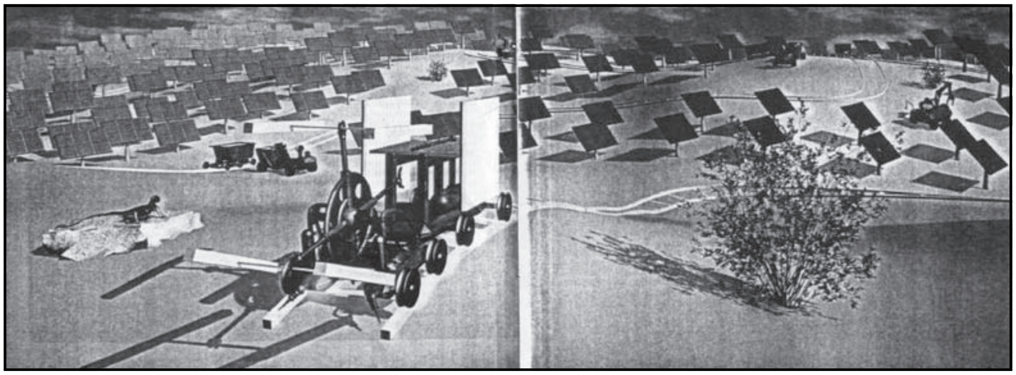


Figure 3.52. A field of constructed solar cells with auxons laying track in foreground. (courtesy of Lackner and Wendt,[1128] illustration by Oko and Mano © 1995 Discover Magazine)

3.15 Lackner-Wendt Auxon Replicators (1995)

Inspired by Dyson's 1970 suggestion[1034] of rock-eating desert replicators (Section 3.6), in 1995 Lackner and Wendt[1128] investigated the possibility of land-based, self-replicating machine systems on Earth: "A minimal system that satisfies the growth requirement would consist of a large solar cell array and a colony of diverse and specialized machines called auxons. With solar energy, raw dirt, and air as its input, the collective purpose of the colony is to expand the solar cell array and build more machines largely without human assistance. Once the desired size is attained, the entire production capacity of the system may be diverted to useful applications such as large scale energy collection, control of greenhouse gases in the atmosphere, and fresh water production."

The colony (Figure 3.52) consists of numerous species of robots, or auxons, including many of the usual functional types that have been mentioned in prior studies of replicating systems. As one reporter[1129] describes it: "Digger auxons scrape an inch of dirt off the desert floor. Transport auxons carry the dirt to a beehive of electrified ovens. Out of these ovens, which work at superhigh temperatures, come useful metals, like iron and aluminum, or the silicon required for making computer chips. Production auxons shape these materials into machine parts and solar panels. Assembly auxons fit them into place." The mobile robots are 10-30 cm in size with a mean lifespan of several growth cycles, are distributed about one every 10 m^2, and run exclusively along an electrified grid embedded in a ceramic track (a ribbed structure 10 cm across in a continuous 1 meter x 1 meter gridwork forming an elevated factory floor) interspersed with 8-meter long, 50-cm wide linear kilns used to manufacture new track segments. The auxon population doubles every 3-6 months. This proposal exemplifies the "factory" or "unit growth" mode of replication manufacturing previously described in Section 3.13.2.2 except that the functional componentry is undifferentiated rather than being separated into distinct sectors of activity.

While "most of the system must be made of common elements," there is no attempt to demonstrate complete materials closure. Elemental abundances of available raw materials are given, but there is no discussion of the specific elemental composition of the auxons themselves or of their supporting infrastructure (e.g., conveyors, crucibles, furnaces, high-temperature thermal sensors, chip-making plant, etc.). Lackner and Wendt outline an interesting method for separating out the 10 most common chemical elements found in raw desert topsoil using a high-temperature (up to 2300 °C) carbothermic process (Figure 3.53), and a limited form of materials processing closure is demonstrated in the sense that all process chemicals are themselves composed of the available 10 elements. The authors admit there are problems with the carbothermic approach — for instance, given the high diffusion rate of gaseous hydrogen "the potential for leakage at 1800 °C is very high",[1128] not

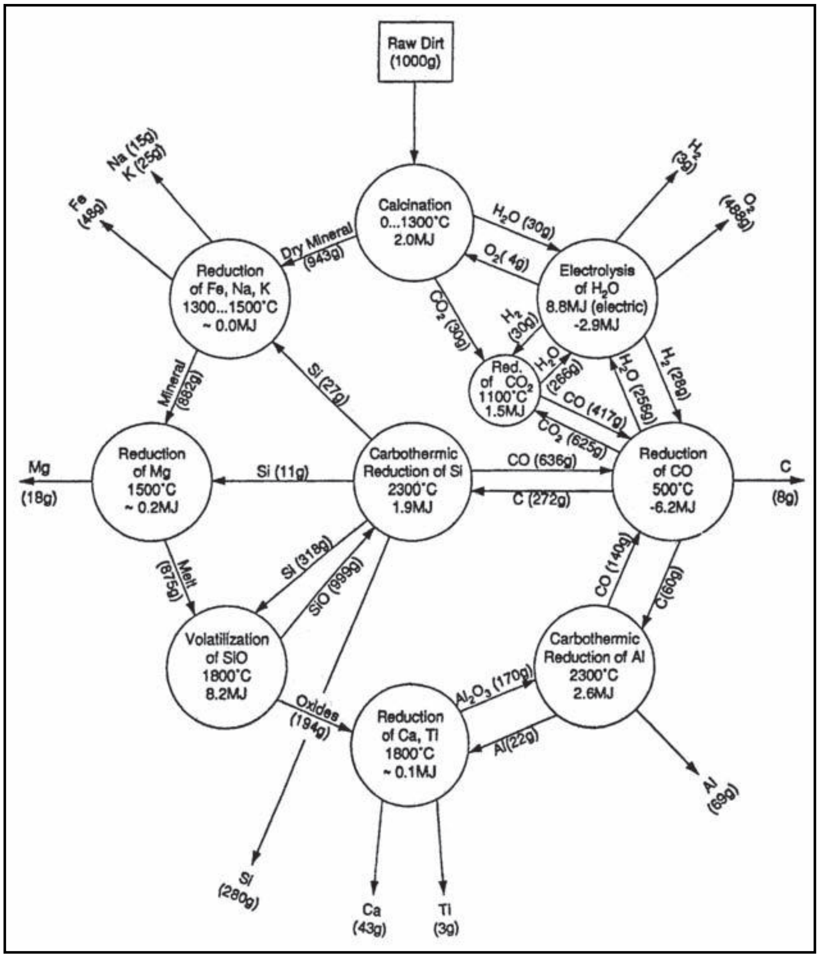


Figure 3.53. Carbothermic element separation cycle for Lackner-Wendt auxons. Processing begins with raw dirt as an input at the top of the figure and proceeds counterclockwise. The products are shown at the outside. With each step is listed the amount of heat which must be added to bring the reactant up to the process temperature and to accomplish the reaction. The heats are normalized to one kilogram of raw dirt. The electrolysis step requires electric energy which is listed separately. (courtesy of Lackner and Wendt[1128])

to mention the potential for explosion in the oxygen-rich terrestrial atmosphere. Other studies[952] have rejected the carbothermic approach in favor of HF (hydrogen fluoride) acid leach[1105,1106] or alternative processes which operate at lower temperatures, leave fewer impurities in the output products, require less insulating materials and generate considerably less waste heat. However, by relying solely on common elements, "it is not necessary to process much more material than is actually to be used in building the system, which would drastically inflate the energy requirements and slow the growth rate of the auxon system."

3.16 The Collins Patents on Reproductive Mechanics (1997-1998)

The natural human urge towards material acquisitiveness has seemingly aspired to its most audacious and complete expression in two patent filings by Charles Michael Collins. Collins is an ambitious inventor who appears, in two patents actually granted by the U.S. Patent Office in 1997[650] and 1998,[651] to have laid claim to the entire design space of artificial kinematic self-replicating machines — or, more specifically, to "the newly named field of science" called "Reproductive Mechanics." The breathtaking scope of the Collins patents is illustrated by the following brief excerpts from the patent filing documents which are of public record.

In his first description of the invention, Collins[650] writes: "The present invention relates to a self-reproducing fundamental fabrication machine (F-Units), such as a high resolution fundamental fabricating unit system or machine having memory and processors for searching, identifying, acquiring, and accessing unlimited types of materials to be used in subsequent manufacturing; and, as well, for making products, other machines including machines of the same type, and ultimately, a fabricating machine that may replicate or reproduce itself as a new machine of the same order. The unlimited materials referred to include materials such as materials provided for acquisition and three dimension processor control with error correction and indices to facilitate the above fabricating and replicating functions in any media. The ultimate fabricating system of the invention in replicating or reproducing itself as a new machine, is an entity of components made capable by the present disclosure of fulfilling these stated objectives within usual and conventional and standard scientific precepts and engineering precepts and yet provides a self-correcting and perfecting feature not found in the prior art." Figure 3.54 shows a schematic view of the basic Collins fabricator, taken from the first patent. While the patents appear not to present a specific workable design for any part of a practical self-replicating system, they may yet provide some inspiration to future engineers.[1130]

Collins[650] expands further: "It is an object of the present invention to provide a machine system that may consist of components having a programmably determined structure defining the arrangement of the components, the system capably reproducing itself according to the programmably determined structure and consisting of fundamental fabricating means for diversely selecting and assembling its components consisting of diverse materials which are at least materials that severally are selected from a group of materials that consist essentially of materials that are electrically insulative, electrically conductive, and substances that are magnetically attractive." Since all materials may be considered as either insulators or conductors, this claim would seem to encompass all known physical building materials.

In the second patent,[651] the claims are further extended to include "a fabrication system for fabricating an object from a plurality of pieces which comprises:

a. a data structure, including related data, representative of the object to be fabricated,
b. at least one first apparatus adapted for reading the data from said data structure,
c. a set of instructions, which utilize the data read from said data structure,
d. at least one second apparatus capable of executing said instructions, and
e. at least one moveable fabrication tool responsive to said instructions, for retrieving said pieces, placing said pieces based on said data of said data structure to form said object and processing said pieces in accordance with said data."

The uses for the patented device would include, among a lengthy list of other things, "quick computer programmable assembly of most any simple object, simultaneous part creation and assembly of small machines, robot creation and upkeep, [and] purifying and perfecting work objects including the environment."

These expansive claims are broadened still further in the second patent,[651] seemingly to encompass the whole of kinematic artificial life: "It is a further object of this invention to provide: a fundamental fabricating machine system...which includes means for locating, purifying, perfecting, acquiring, metabolizing and assimilating sustenance in the environment with less symbiotic necessity than most natural present life forms, and, by way of a new means similar to robotics that is hereinafter newly named and claimed and coined herein as the newly named field of science 'Reproductive Mechanics' execute unitized reproduction of itself with no help from man after man has first created it and its

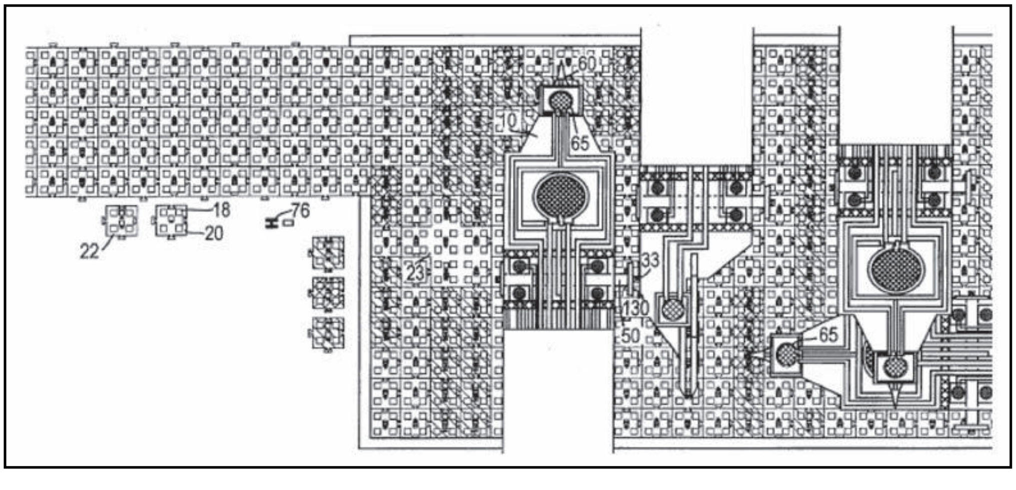


Figure 3.54. Plan view of a system comprising a self-reproducing fundamental fabricating machine. (from Collins [650])

systems and accessories, executing reproduction of its own needed living environment making it more cause than effect, having intellectual direction and purpose and acting in the direction of its own propagation and man's and other life forms, adapting to the environment around it, being sensory and communicating with itself and/or man and/or computers, having reproducible and updateable memory with chaining capability and repeatable series and parallel operations with qualifications, and having a potentially infinite group life-span for providing thereby a man-made, evolutionary artificial life."

Collins' patented device "is by design an entity that endeavors to solve all man's problems, physical and intellectual, with the shortest paths to these ends built in interactively as an intrinsic characteristic....As it further evolves within these aforestated primary directives the only thing left to be done (which it can do) is go about evolutionary improvements in the quality and quantity of its appointed tasks. Physical and intellectual self-reproductivity with improvement is the important feature that brings about this important aforestated state of affairs. Evolutionary programming which in this medium alters full change of shape and size in all parameters will eventually reduce the paths, between the intellect and the physical task, to a virtually negligible minimum so it (the F-Unit 10 and system) will be ultimately all that is necessary as virtually all man's tasks will be efficiently handled for all within the physical plane; with the only exceptions being tasks done over large (planetary) distances."

As a final legal catch-all in the unlikely event that some tiny corner of the kinematic replicator design space has been inadvertently omitted, the second patent[651] warns: "The foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described except where specifically claimed, and accordingly, all suitable modifications and equivalents may be resorted to as falling within the scope of the claims."

Replicating systems engineers who, upon reading the above, might become concerned that their existing or future inventions could infringe the Collins patents, should take note that the disclosures of prior art attested in both patent filings[650,651] include not a single reference to von Neumann's substantially identical prior work (beginning in 1948; Section 2.1.2). Astonishingly, von Neumann's name appears nowhere in any of Collins' documents, nor is there a single mention of any of the many hundreds of items of previously published relevant literature that are cited elsewhere in this book. These fatal omissions should have significant implications for the future viability and enforceability of the Collins patents.

In the field of kinematic self-replicating machines, the most directly relevant U.S. patents seem to include (with quoted abstracts) the following:

- **U.S. 4,734,856 "Autogeneric system" (March 1988)**:[1131] The invention of the "autogeneric system" is a closed recursive manufacturing cycle. The working model operates by the relentless application of directed trial and error. The copyrighted version can be used to manufacture microcomputer systems, and process control systems. The value of "autogeneric systems" rests in the inherent ability to create or manufacture complex systems on demand. The autogeneric system has been doubling in size and complexity about every three months while in use. One practical development has been the "Silicon Scribe," a device that manufactures single chip computers from high level specifications. The autogeneric system has been used to bootstrap from a crude interpreter that operated on virtual machine instructions to the "archive," a self replicating computer manufacturing system.
- **U.S. 5,659,477 "Self reproducing fundamental fabricating machines (F-Units)" (August 1997):**[650] First Collins patent; see above.
- **U.S. 5,764,518 "Self Reproducing Fundamental Fabricating Machine System" (June 1998):**[651] Second Collins patent; see above.
- **U.S. 6,510,359 "Method and system for self-replicating manufacturing stations" (January 2003):**[273] A system and method which provide a non-biological self replicating manufacturing system ("SRMS") are disclosed. A preferred embodiment provides an SRMS that enables assembly stations to replicate. In a preferred embodiment, positional assembly is utilized by one or more assembly stations to construct like assembly stations. Furthermore, in a most preferred embodiment, such assembly stations are small scale devices that are capable of working with small scale parts, such as micron-scale, nanometer-scale or even molecular-scale parts, in order to construct like assembly devices. The SRMS of a preferred embodiment performs surface-to-surface assembly. For example, an assembly station on a first surface (e.g., wafer), Surface A, constructs a like assembly station on another surface (e.g., wafer), Surface B. Most preferably, the assembly stations replicate at an exponential rate. (The Zyvex Rotapod™ approach to "exponential assembly"; Section 4.17).
- **U.S. 6,521,427 "Method for the complete chemical synthesis and assembly of genes and genomes" (February 2003)**:[1132] The present invention relates generally to the fields of oligonucleotide synthesis. More particularly, it concerns the assembly of genes and genomes of completely synthetic artificial organisms. Thus, the present invention outlines a novel approach to utilizing the results of genomic sequence information by computer directed gene synthesis based on computing on the human genome database. Specifically, the present invention contemplates and describes the chemical synthesis and resynthesis of genes defined by the genome sequence in a host vector and transfer and expression of these sequences into suitable hosts. (The Egea biorobotics approach; Section 4.4).

Other possibly relevant or interesting U.S. patents include:

- *U.S. 4,575,330 "Apparatus for production of three-dimensional objects by stereolithography" (March 1986):*[1197] A system for generating three-dimensional objects by creating a cross-sectional pattern of the object to be formed at a selected surface of a fluid medium capable of altering its physical state in response to appropriate synergistic stimulation by impinging radiation, particle bombardment or chemical reaction, successive adjacent laminae, representing corresponding successive adjacent cross-sections of the object, being automatically formed and integrated together to provide a step-wise laminar buildup of the desired object, whereby a three-dimensional object is formed and drawn from a substantially planar surface of the fluid medium during the forming process. (See Section 3.20.)
- *U.S. 4,608,525 "Cellular type robot apparatus" (August 1986):*[1133] This invention relates to a cellular type robot apparatus consisting of a plurality of robot cells each having intelligence, wherein each robot cell controls its own operation on the basis of information exchange with adjacent robot cells. The operations of the robot cells are as a whole coordinated, and each robot cell can be controlled without the necessity of change of hard- and soft-wares even when one or more of the robot cells are out of order or when the robot needs to be expanded. Each robot cell can be provided so that the robot can be increased or decreased

in a building block arrangement. More definitely, each robot cell has arms corresponding to hands and feet, and is able to control its own operation. As the robot cells are connected and combined through transmission routes so as to be able to exchange information, they can operate cooperatively as a group to perform a manipulative action. The operation of the group of robot cells is designed also to constitute the shape of a predetermined pattern besides the operations of entwining an object, and gripping and moving the object. (See Section 3.8.)

- *U.S. 4,835,450 "Method and system for controlling robot for constructing products" (May 1989):*[1134] A 3-dimensional form of a sample product constituted by a plurality of parts having known forms is measured by imaging the sample product from a plurality of directions. Arrangement data representing the 3-dimensional positions and orientations of the parts constituting the sample product are obtained, by a construction detecting module, on the basis of the measured 3-dimensional form of the sample product. A task planning module sets a task for moving a part to be used for constructing a product and the sequence of the task by using arrangement data acquired by the construction detecting module. Upon generation of motion command data for controlling a robot for constructing the product in accordance with the task set by the task planning module, the generated motion command is output to a motion control module. The construction robot is controlled by the motion control module, whereby a product the same as the sample product is constructed.
- *U.S. 4,964,062 "Robotic arm systems" (October 1990):*[1135] A multisection flexible multidigit arm contains hands at each end, each of which hands contains a set of fingers, suitably three, which are similarly formed flexible multidigit arms constructed to a smaller scale. Each hand contains connectors for coupling the hand to a mating connector mounted on an associated structure to provide appropriate power and control signals to the arm. One hand may grip the connector and the other hand is free to move to various positions and perform various tasks. In an additional aspect the arm may move to different locations by somersaulting between spaced connectors in the system. In an assembly system the robotic arms are used to construct frames or other assemblies. A completely self contained arm includes a self contained source of power. Radio communication means are provided to allow electronic interaction with the arm from a remote location. In an additional aspect the self contained circuitry includes processor means programmed to control the arm to perform a certain task, relieving the operator at the remote location from specifying the details. Control signals to the sections of the arm in an additional aspect to the disclosed invention are provided by an electrical system that uses only a few wires by multiplexing the signals and the actuators, effectively "time sharing" the electrical leads between the large number of actuators.
- *U.S. 5,150,288 "Production management system and method of transmitting data" (September 1992):*[1136] A production management system for controlling a production line such as an automobile assembling line includes a plurality of slave computers for controlling assembling robots in assembling stations, and a host computer for supervising common information required by the slave computers. When the common information is to be modified due to a change in the robots, the common information stored in the host computer is modified into corrected common information, and the corrected common information is transmitted from the host computer to the slave computers. The common information stored in the slave computers can therefore be modified by the corrected common information.
- *U.S. 5,210,821 "Control for a group of robots" (May 1993):*[1137] A control for robots wherein a plurality of control units are connected in a hierarchical structure including a plurality of ranks including the lowest rank, and the robots subordinate to the control units belonging to the lowest rank. The present invention relates to a control for a group of robots, each having a plurality of mobile axis drive mechanisms, which are assigned to perform a variety of functions to assemble a product, and more particularly to a control arrangement which makes it easy to locate malfunctions developing in the robots.
- *U.S. 5,214,588 "Control apparatus for an FMS line" (May 1993):*[1138] A control apparatus provided for an FMS (flexible manufacturing system) line having a robot for carrying a workpiece and an AGV (automatically guided vehicle) for carrying a jig to be coupled to the workpiece. The control apparatus generally includes a production instruction device and an AGV movement control device. The production instruction device determines a schedule for supplying jigs on the basis of a work supply order schedule. The AGV movement control device causes an AGV to skip an unavailable station and to move to an available station in accordance with the presence or absence of a workpiece and/or a jig and a kind of a cell to which the AGV is to be moved. The robot operates continuously in the order of the disposition of cells.
- *U.S. 5,283,943 "Automated assembly apparatus" (February 1994):*[1139] A method and apparatus for assembling multiple component products using automated assembly equipment having predetermined locations for loading of components or component compartments. The invention includes a component identifier which reads indicia of component identity from components or component compartments, and a location indicator which indicates a proper location for loading and identified component or component compartment. The invention also contemplates a sensor that senses the placement of components or component compartments in the locations of the assembly machine, and a disabling device which disables the assembly machine if components or component compartments are misplaced.
- *U.S. 5,355,577 "Method and apparatus for the assembly of microfabricated devices" (October 1994):*[1338] A method of rapidly assembling many discrete microelectronic or micro-mechanical devices in a precise configuration. The devices are placed randomly on a template consisting of a pair of oppositely charged planar electrodes. The upper electrode contains a multiplicity of apertures. The template is vibrated and the devices are attracted to the apertures and trapped thereat. The shape of a given aperture determines the number, orientation, and type of device that it traps. The process is completed by mechanically and electrically connecting the devices. The present method for self-assembly allows many sub-millimeter sized electronic components or other particles to be rapidly assembled into a predetermined configuration.
- *U.S. 5,390,283 "Method for optimizing the configuration of a pick and place machine" (February 1995):*[1140] A genetic algorithm is used to search for optimal configurations of a computer controlled pick and place machine, which places parts on printed circuit boards. Configurations include: assigning grippers to pipettes of the machine; assigning parts, destined for the printed circuit boards, to feeders of the machine; assigning parts to pipettes; and determining time intervals and orders in which parts are to be placed. The genetic algorithm is applied to chromosome strings representing parameters for determining machine configuration. A heuristic layout generator generates machine configurations from the chromosome strings.

- *U.S. 5,390,282 "Process for problem solving using spontaneously emergent self-replicating and self-improving entities" (February 1995):*[373] An apparatus and process for solving problems using self-replicating and self-improving entities. The present invention includes an apparatus and process for solving a problem using a population of entities, wherein each of the entities is an arrangement of actions and material which are capable of including an incorporation action and are capable of including an emission action. (See Section 2.2.1.)
- *U.K. GB19940004227, U.S. 6,157,872, "Programmable materials" (U.K. September 1995, U.S. December 2000):*[816] Programmable material is a collection of substantially cubic shaped bricks called monomers that move relative to each other under computer control to sculpt engineering structures and mechanisms (walking machine). The monomers have features to lock to other monomers and slide relative to other monomers without separating. The monomers are fault tolerant against damage; functional monomers move faulty monomers and replace them with functioning clones. Movement of monomers is broken down systematically into streamers, gateways, highways and reservoir methods to obtain individual monomer movement paths required to synthesize a structure. Specialized monomers can carry tools which together with synthesis of custom structures create custom machines. (Joseph Michael's "fractal robots"; Section 3.8.)
- *U.S. 5,468,851 "Construction of geometrical objects from polynucleotides" (November 1995):*[1141] One, two and three dimensional structures may be synthesized or modified from polynucleotides. A core structure is expanded by cleavage of a loop with a restriction endonuclease and ligating another polynucleotide to the sticky ends so that the recognition site of the restriction enzyme is not reformed. This process is repeated as many times as necessary to synthesize any desired structure. The structures formed have a wide range of uses. (Seeman's DNA-based structures; Section 4.5.)
- *U.S. 5,475,797 "Menu driven system for controlling automated assembly of palletized elements" (December 1995):*[1142] The present invention is a method and apparatus for defining the critical characteristics of a pallet, or tray, used to supply workpieces to an automated, flexible assembly station or workcell. Once the characteristics are described and stored in memory, they may be used to uniquely identify workpieces which are determined to be defective during the automatic assembly operations.
- *U.S. 5,508,636 "Electronic system organized as an array of cells" (April 1996):*[1143] The invention concerns a programmable integrated electronic system including an array of identical cells. Each cell includes functional components capable, when they are correctly connected, of executing a given function, and programmable connecting means for on the one hand connecting the functional components to each other and on the other hand connecting the cell to its neighbors. The present invention is characterized in that the system includes means of storing a first data item which defines the function of each of the cells in the array and in that each cell has means for extracting, from this first data item and its location the network, the programming word for its own function. In addition, means are provided for effecting the test of correct functioning of each cell and for reconfiguring the array where there are defective cells.
- *U.S. 5,539,975 "Control system and equipment configuration for a modular product assembly platform" (July 1996):*[1144] A modular product assembly platform which includes a multiple number of industrial robots or other similar assembly devices. The product assembly platform also includes a programmable controller system housed in a logic control cabinet, a vision control system housed in a vision control cabinet and a set of robot controllers which operate together to control the robots or assembly devices for performing product assembly tasks.
- *U.S. 5,586,387 "Automated part assembly machine" (December 1996):*[1145] An automated part assembly machine has a work table supported to a base and movable relative thereto and at least two separate robots each having an end effector movable around within an individual work region. The two robots are positioned in such a relation as to give a common work region in which the individual work regions of the two robots overlap. A parts supply is arranged to the work table for storing parts to be picked up by the robots. A plurality of operator hands are selectively and removably attached to the end effector of the robot for handling the parts by the robot. Disposed within the common region is a jig which positions the parts for assembly by the robot. The robots and the work table are controlled to operate in cooperation for assembly of the parts. The robots are enabled to move together with the jig and the operator hands relative to the parts supply so that the robots can reach over a wide range of the parts supply beyond the individual work regions to thereby successfully pick up suitable parts and transfer them to the jig for immediate assembly of the parts. Further, since the operator hands are on the movable work table, the robot can change the operator hands while moving relative to the parts supply for effecting the part assembly substantially without interruption, in addition to the advantage of enabling one robot to change the operator hand while the other robot is handling the parts.
- *U.S. 5,717,598 "Automatic manufacturability evaluation method and system" (February 1998):*[1146] A designed object workability evaluating system for evaluating quantitatively at a stage of designing an article whether a structure of the article as designed can be realized easily in a manufacturing stage for thereby selectively determining a best structure from a plurality of design plans through comparative evaluation thereof. A server machine section includes a registering unit storing evaluation elements defined by the user, an index calculating module for calculating indexes indicating degrees of difficulty/ease of work, an evaluation element estimating module, a part workability evaluation module, an article workability evaluation module, and a best design plan selection/determination module.
- *U.S. 5,835,477 "Mass-storage applications of local probe arrays" (November 1998):*[1147] The present invention concerns a storage device comprising a local probe array and a storage medium with an array of storage fields (pits on surface). The local probe array is situated opposite to the storage medium such that each local probes of the local probe array can be scanned over the corresponding storage field. (The scanning-probe array or Millipede concept; Section 5.7.)
- *U.S. 5,980,084 "Method and apparatus for automated assembly" (November 1999):*[1148] This invention relates to the field of assembly of mechanical systems, specifically automated planning of a sequence of steps for assembly or disassembly of a mechanical system comprising a plurality of parts. A process and apparatus generates a sequence of steps for assembly or disassembly of a mechanical system. Each step in the sequence is geometrically feasible, i.e., the part motions required are physically possible. Each step in the sequence is also constraint feasible, i.e., the step satisfies user-definable constraints. Constraints allow process and other such limitations, not usually represented in models of the completed mechanical system, to affect the sequence.

- *U.S. 5,988,845 "Universal unit for automatically configuring three-dimensional structures of a desired shape" (November 1999):*[1149] A three-dimensional universal unit includes multiple identically configured assembly units, each having a central unit body, arms that can rotate relative to the unit body, the arms extending from the unit body in three orthogonal axes and having a connecting mechanism at the end of each arm. The assembly unit also has an information processing unit for controlling a motor in the unit body, an assembly unit operation, a rotary drive transmission system for transmitting arm drive motion from the motor, and a drive transmission system for engaging and disengaging the connecting mechanisms. Each connecting mechanism can mechanically connect with a connecting mechanism of another assembly unit and includes a communication device for exchanging information between information processing units of connected assembly units. (Another KCA system; Section 3.8.)
- *U.S. 5,994,159 "Self-assembling micro-mechanical device" (November 1999):*[2447] A self-assembling micron-sized mechanical device is described. The device comprises hinged plates attached to a support. A beam having a first end free to move in an upwardly-directed arc is associated with each hinged plate comprising the device. The beam has a first engagement member, including a first angled edge, disposed at its freely-movable first end. Each hinged plate includes a second engagement member, including a second angled edge. In the unassembled state, at least a portion of the first engagement member lies beneath the second engagement member on the support. Actuation force is applied to the beam by an actuator, the force causing the first end of the beam to lift. As it does so, the first and second angled edges slide over another, and the hinged plate is rotated upwardly about its hinges away from the support. The mechanical advantage provided by the angled edges allows a hinged plate to be rotated fully ninety degrees away from the support. (Another example of "micro-origami" (Section 4.1.5), as is the work by Hui et al[1150]). Kris Pister first demonstrated silicon hinged plates in 1992[2445] but the University of California at Berkeley did not pursue a patent.
- *U.S. 6,072,044 "Nanoconstructions of geometrical objects and lattices from antiparallel nucleic acid double crossover molecules" (June 2000):*[1151] Two- and three-dimensional polynucleic acid structures, such as periodic lattices, may be constructed from an ordered array of antiparallel double crossover molecules assembled from single stranded oligonucleotides or polynucleotides. These antiparallel double crossover molecules have the structural rigidity necessary to serve as building block components for two- and three-dimensional structures having the high translational symmetry associated with crystals. (Seeman's DNA-based structures; Section 4.5.)
- *U.S. 6,142,358 "Wafer-to-wafer transfer of microstructures using break-away tethers" (November 2000):*[1152] Break-away tethers to secure electronic, mechanical, optical, or other microstructures, during release from one substrate and transfer to another. Microstructures are fabricated with integrated tethers attaching them to a first substrate. The structures are undercut by etching and contacted and bonded to a second substrate. First and second substrates are separated, breaking the tethers. (Relevant to MEMS positional assembly; see Section 4.17.)
- *U.S. 6,200,782 "Construction of nucleoprotein based assemblies comprising addressable components for nanoscale assembly and nanoprocessors" (March 2001):*[1153] A logical next step in biotechnology is the fabrication of assemblies and devices on the nanometer scale. Since most devices take advantage of the proximity and precise 3-D arrangement of individual components, one of the limitations in the fabrication of nanoscale devices has been the inherent lack of specificity in chemical methods for addressing components like bioengineered proteins to precise locations in a 2-D array or 3-D lattice. Herein, a nucleoprotein based nanoprocessor is described. The nanoprocessor includes one or more chimeric fusion proteins linked to a DNA scaffold. Both components of the fusion protein are enzymes. (See Section 4.5.)
- *U.S. 6,205,362 "Constructing applications in distributed control systems using components having built-in behaviors" (March 2001):*[1154] A distributed control system including self-organizing components which are preselected on the basis of built-in behaviors which are needed to perform a particular application. The built-in behaviors enable the components to automatically self-organize and perform the application once coupled to the network.
- *U.S. 6,233,502 "Fault tolerant connection system for transiently connectable modular elements" (May 2001):*[1155] A system and method for transiently connecting modular elements of a self-movable robot. The self-movable robot is known as metamorphosing robots, polymorphic robots, shape-changing robots, or morphable structures. The modular elements can act together to build a structure to perform a given task. Each robotic module contains a mechanism allowing for communication and transfer of power between adjacent modules, and defining a robot whole to be all the modules in one connected component. (Another KCA system; Section 3.8.)
- *U.S. 6,535,786 "Modular automated assembly system" (March 2003):*[1156] A method of modular manufacturing is disclosed and a modular assembly system is shown utilizing a base unit and a plurality of detachable work stations adapted to operate with the base unit. Each detachable work station includes its own work station control processor. The assembly system is preferably fully modular since each work station is capable of controlling its own operation. Work stations may be plugged into a plurality of different work station ports on the base unit in a plurality of different combinations, preferably without reprogramming either the base unit control processor or the work station's control processor.

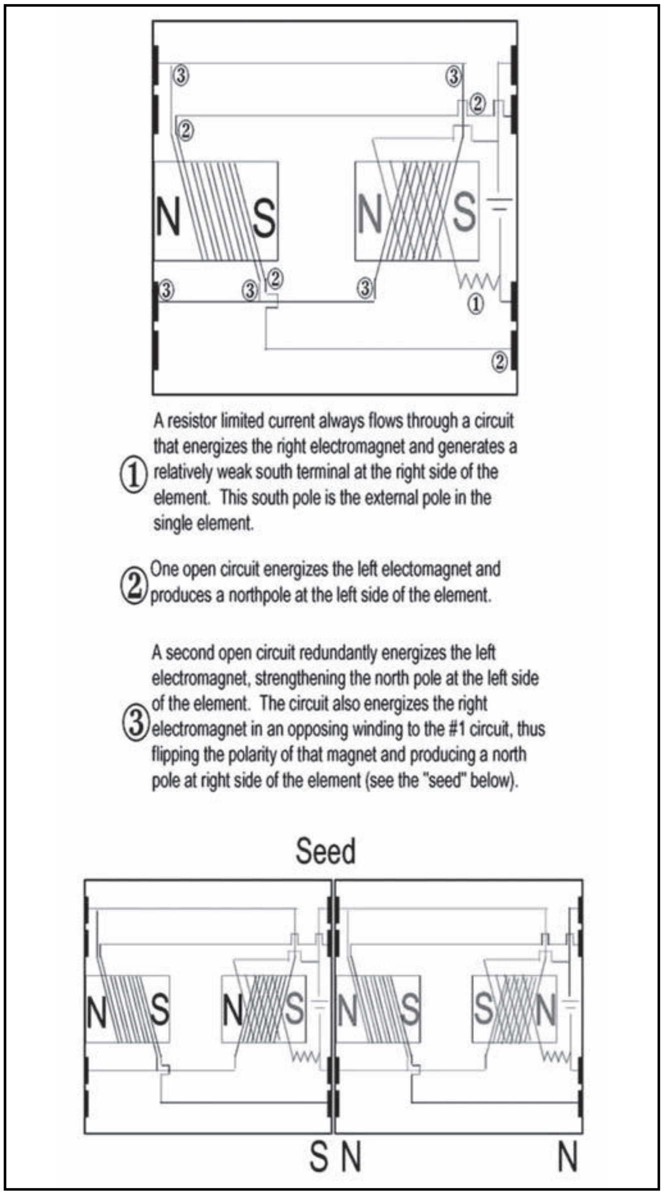
3.17 Lohn Electromechanical Replicators (1998)

Following in the spirit of the simple early devices of Penrose (Section 3.3) and Morowitz (Section 3.5), in 1998 Lohn et al[1157] presented designs for two simple electromechanical replicators that could be constructed out of plastic, batteries and electromagnets. Following the invariant design principles exemplified by earlier devices, Lohn's systems draw analogy from chemistry, with electromagnetic forces modeling molecular bonding, complementary physical shapes modeling molecular structure, and electrical current flow modeling activation. Lohn notes that "designing a self-assembling structure is akin to engineering an artificial catalyst, where a specific event becomes likely only in the presence of specific components. This problem appears simple but is deceptive: it is not very difficult to engineer the self-assembly process where a parent structure attracts the necessary components, assembles them, then detaches from the offspring structure. The difficulty lies in ensuring robustness. One must prevent the possibility of blocked active sites, cancerous growths, crystal-growth formations, and other deleterious side effects that may occur when components are randomly interacting."

Lohn follows Penrose's ground rules[681] which define a "seed" structure as self-replicating if it can induce the formation of two or more new structures which are identical to itself and which are assembled by combining simpler components already present in the environment: "Assume we have a two-dimensional environment in which components are mobile (e.g., coins placed between two parallel plates of glass). If we populate the environment with numerous components, add energy to it (e.g., by shaking), and wait, we expect the initial and final configurations of the system to be similar — randomly placed components. However, if we place a self-assembling seed structure into the initial environment, then add energy, we would expect to see multiple seed copies appear over time, with a corresponding decrease in the number of free components."

Lohn's two electromechanical models — the first a seed composed of two identical components, the second a seed composed of two distinct components — are inspired by Morowitz's 1959 model[688] (Section 3.5) while making the design simpler using only active components. Lohn's designs have no mechanical linkages between components and consist solely of circuits, whereas the Morowitz model relies on two sliding parts to operate two switches. All of Lohn's components are active, whereas Morowitz' model used one active and one passive component. Finally, Lohn's components have no explicit switches — circuits are switched on and off via the bonds that form between components — and his designs require one battery rather than two. Both devices are intended to replicate when placed in a "sea" of parts jostling on an agitated planar surface.

Lohn Monotype Electromechanical Replicator. The monotype replicating seed consists of two identical components, each consisting of a pair of electromagnets cross-wired through a set of contacts, a resistor, and a battery (Figure 3.55). All parts adhere solely by magnetic attraction. Replication proceeds as follows (Figure 3.56): (I) The monotype seed is formed by forcing two elements (each with only one exposed south terminal) together. (II) Forming the seed closes contacts that flip the polarity of the rightmost electromagnet and energizes the second electromagnet in the same (left) element, locking the two "seed" elements. The south terminal of a single element is attracted to the newly energized north "seed" terminal. (III) The new threesome closes circuits that strengthen the existing charges and energize the leftmost electromagnet, exposing a north terminal. As in the previous step, a single element is attracted to the exposed north terminal. (IV) The attachment of the fourth element closes a circuit that flips the sign of the middle-left electromagnet (parallel to the original seed formation) causing the arrangement to become unstable. The two north terminals in the center of the foursome now repel each other. (V) The final result is a new 2-element seed in addition to the first 2-element seed. Over time the single elements with an exposed south terminal are transformed into 2-element "seeds" with a north terminal exposed.



① A resistor limited current always flows through a circuit that energizes the right electromagnet and generates a relatively weak south terminal at the right side of the element. This south pole is the external pole in the single element.

② One open circuit energizes the left electomagnet and produces a northpole at the left side of the element.

③ A second open circuit redundantly energizes the left electromagnet, strengthening the north pole at the left side of the element. The circuit also energizes the right electromagnet in an opposing winding to the #1 circuit, thus flipping the polarity of that magnet and producing a north pole at right side of the element (see the "seed" below).

Figure 3.55. Lohn monotype electromechanical replicator: a single-type component (top) and two-component seed unit (bottom).[1157] (courtesy of Jason Lohn/NASA)

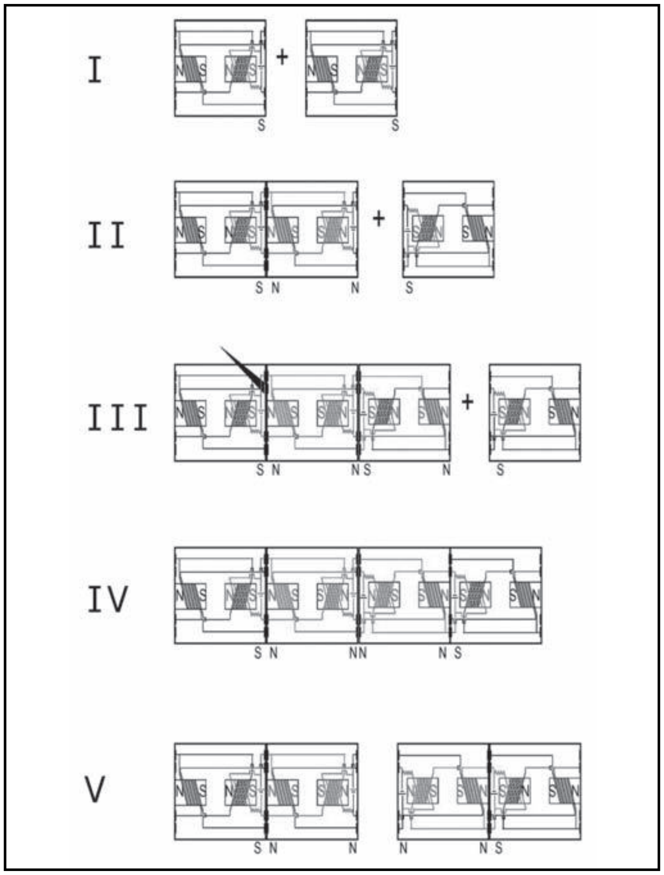


Figure 3.56. Lohn monotype electromechanical replicator: self-assembly steps.[1157] (courtesy of Jason Lohn/NASA)

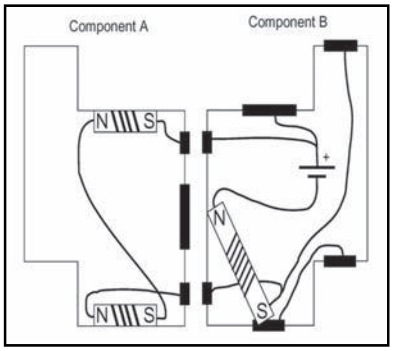


Figure 3.57. Lohn polytype electromechanical replicator: two component types comprise a single seed unit.[1157] (courtesy of Jason Lohn/NASA)

Lohn Polytype Electromechanical Replicator. The polytype replicating seed consists of two distinct components (Figure 3.57). The first component is a pair of electromagnets wired to a set of contacts. The second component is a single electromagnet and a battery wired to a different set of contacts. Again, all parts adhere solely by magnetic attraction. Replication proceeds as follows (Figure 3.58): (I) The polytype seed forms via random collision or by artificial introduction; circuit 1 is energized forming a bond between components A and B. (II) When immersed in a sea of individual components, only component B is biased towards attaching to the AB complex; an attractive force and complementary shapes encourage B to attach. (III) Likewise, the AB-B complex encourages component A to attach as shown. (IV) Once attached, the lower AB complex is energized, and the resulting repellant force pushes the offspring complex away from its parent.

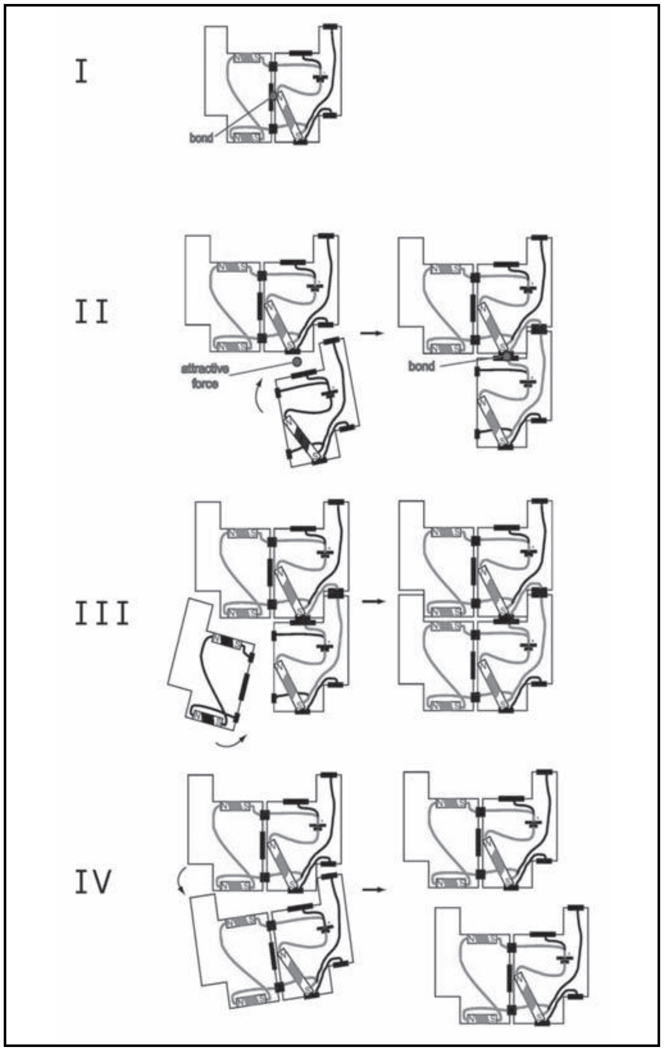


Figure 3.58. Lohn polytype electromechanical replicator: self-assembly steps.[1157] (courtesy of Jason Lohn/NASA)

Lohn and his colleagues attempted to build both models from scratch, winding the specialized electromagnets by hand, but were unable to complete these constructions due to serious limitations in the time and resources available.[1158] The authors of this book can see no reason why Lohn's models, if physically implemented, would not work. Lohn et al[1157] conclude: "The electromechanical models presented here represent one medium in which self-assembling machines can be studied. The future of designing such models for nanotechnology will likely benefit from work in many disciplines, ranging from biochemistry to physics to artificial life. Because designing self-assembling systems is non-trivial, automating the design process[371] may hold great benefit. Furthermore, automated approaches may create self-assembling systems that embody principles human designers would never think of."

3.18 Moses Self-Replicating Construction Machine (1999-2001)

During 1999-2001, Matt Moses, a graduate student in the Department of Mechanical Engineering at the University of New Mexico, invented a unique set of Lego-like blocks that are especially well-suited for the self-replication task and elaborated some of the detailed kinematic requirements of a machine that can self-replicate or assemble its own duplicate from a stock of components.[915,1159] The Lego-like components were plastic parts that were cast from a polyurethane resin and then used to make a 3-axis Cartesian manipulator which was subsequently shown to be kinematically capable of assembling a duplicate of itself. The machine cannot fabricate its own plastic components and — in addition to mechanical problems that hamper the physical device — the constructor must be controlled by an external entity. To be fully self-replicating, says Moses,[915] the device would have to autonomously control its own actions and would have to possess the instructions necessary for carrying out its duplication. "The ultimate goal of this work is the creation of a machine that can automatically fabricate components from raw materials and then assemble these components into a wide range of useful devices, including duplicates of the original machine."

Figure 3.59(A) shows two exploded views of Moses' "basic component." The component consists of two parts — an upper "handle" and a lower "base". The base contains four compliant snap tangs that are complementary to the four tapered surfaces of the handle. Blocks can be assembled together as shown in Figure 3.59(B), which also shows how the snap tangs of the base will grasp the undercut of the handle of another part. In addition, the convexly tapered surfaces of the base mate with concavely tapered surfaces of the handle in order to provide rigidity with respect to shear and torsion between parts. Most edges on the handle and base are chamfered. The chamfers are important because they allow a certain amount of positioning error during assembly. The tangs and handle also contribute to error tolerance, since they are tapered such that two parts need not be exactly positioned before assembly. The slots cut in each side of the base allow the part to be assembled onto other parts that have reinforcing segments. Depending on the type of loading on the tang, it will bend primarily in either the upper or lower segment of the 'L'. This can be exploited so that parts can

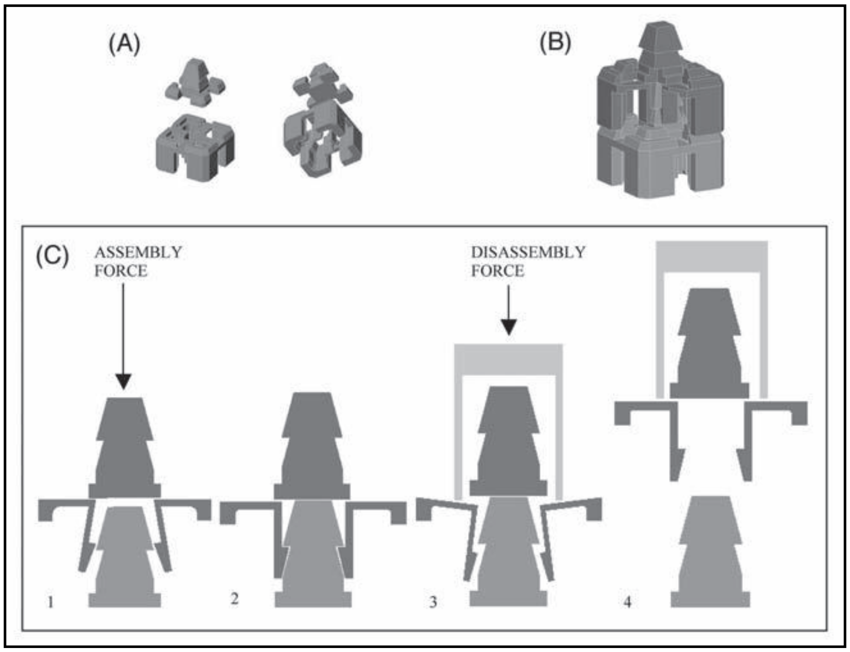


Figure 3.59. Moses' "basic component" for self-replicating construction machine. (A) Exploded views of basic component. (B) Two assembled components, cutaway view. (C) When two parts are assembled, the tangs of one part bend outward to clear the handle of the other part. One way the parts can be disassembled is if a tool depresses the tangs of a part so that they can clear the handle of the other part. (courtesy of Matt Moses[915])

be disassembled. In other words, the snap-assembly is reversible. Figure 3.59(C) shows a sequence of sectioned views of two parts during assembly and disassembly.

A plane surface can be tiled by the parts, resulting in a plane covered by periodically spaced handles. The constructing machine described here operates on such a plane. Part type 3 (Figure 3.60(A)) is identical to part type 2, except that its top handle has been replaced with a rotary handle. A second type of connection between parts is the handle-slider connection. The slider — a long beam with the same cross section as a snap-tang — allows a part to slide back and forth along the handles of other parts, as in Figure 3.60(B) which shows a rack assembled onto the operating plane. By adding an actuator, forces can be applied to moving parts and their positions can be controlled. In this component set there are two types of motors — a rotary type and a linear type. Racks are actuated by rotary motors. The rotary motors are made by attaching a basic part and a drive gear to an off-the-shelf motor. The rack and the drive gear have self-aligning teeth (the teeth easily mesh) in order to simplify assembly. In Figure 3.60(C), a motor has been added to the assembly.

Moses' constructing machine is built out of 45 parts, including 11 different kinds of parts (all meticulously described in his thesis[915]), as follows: Rack (8 used in constructing machine), Motor 1 (1 used), Anchor (7), Rail (13), Cap (8), Rotary Cap (1), Cross-member (3), Cap with Support (1), Cross-member with Support (1), Motor 2 shown in Figure 3.60(D) (1), and Motor 3 shown in Figure 3.60(E) (1). Five other parts (Basic Part, Plane Element, Rotary Plane Element, Small Gear (11 teeth), and Large Gear (14 teeth)) are not used in the constructor but could be incorporated into devices that the constructor could assemble. Addressing tradeoffs in designing parts sets, Moses[915] explains: "These 'universal' components are not all that universal — some of the parts are used in large numbers, while other special-purpose components are used infrequently. It is possible that an optimally designed component set would contain only a few types of parts, and these parts would find more uniform use in an assembly. Keep in mind, however, that there is a tradeoff between the complexity of the set itself and the complexity of an assembly made from it. Making a given assembly from a set of simple components may necessitate the use of many more parts than would be required when making an equivalent assembly from a set that had an extra few special-purpose components."

Moses continues: "The component set was designed in an iterative process. During this process, there was no clear design for the constructor. New functionalities were simply added to the set until the parts could be made into a suitable manipulator. This aimless wandering through design space is often time-consuming and costly. Suh[1160] presents a systematic approach to design wherein a hierarchy of functional requirements (*what* a system must do) and design parameters (*how* it will do it) are evaluated based on two axioms: (1) Maintain the independence of functional requirements. (2) Minimize the information content of the design (keep it simple). The functionality matrix (Figure 3.61) for the component set [makes] clear...that not all functional requirements are independent, and also that in some cases many parts satisfy the same requirement." A functionality matrix can be used to compare structures, components, or features of a design with the functions they perform.

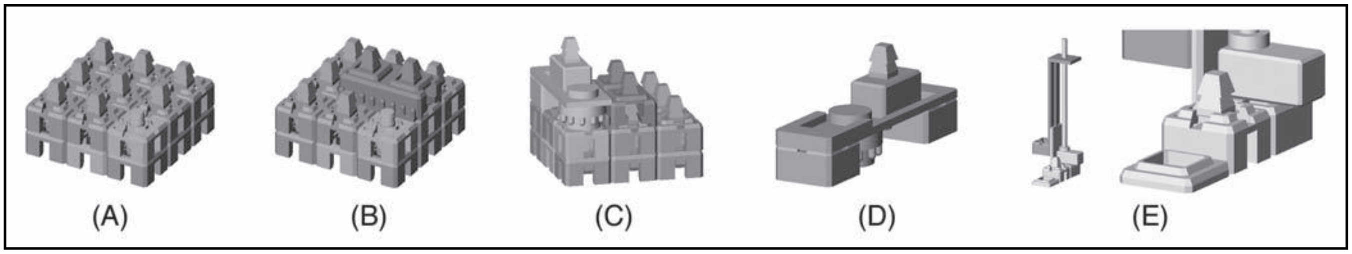
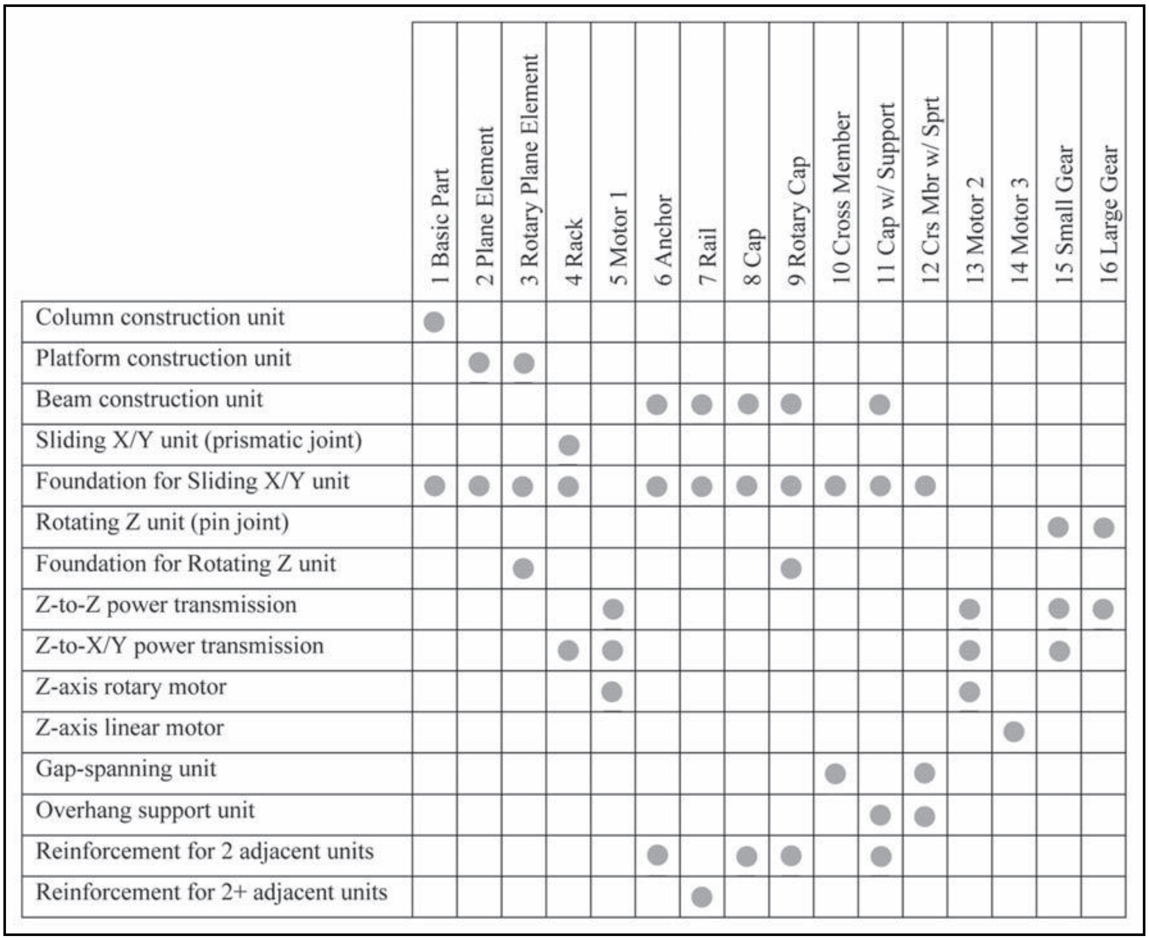


Figure 3.60. Moses' component assemblies for self-replicating construction machine. (A) A simple operating plane. (B) an assembly with a moving part. (C) a motorized assembly. (D) Motor 2. (E) Motor 3 (full view at left, closeup at right). (courtesy of Matt Moses[915])



	1 Basic Part	2 Plane Element	3 Rotary Plane Element	4 Rack	5 Motor 1	6 Anchor	7 Rail	8 Cap	9 Rotary Cap	10 Cross Member	11 Cap w/ Support	12 Crs Mbr w/ Sprt	13 Motor 2	14 Motor 3	15 Small Gear	16 Large Gear
Column construction unit	●															
Platform construction unit		●	●													
Beam construction unit						●	●	●	●		●					
Sliding X/Y unit (prismatic joint)				●												
Foundation for Sliding X/Y unit	●	●	●	●		●	●	●	●	●	●	●				
Rotating Z unit (pin joint)															●	●
Foundation for Rotating Z unit			●						●							
Z-to-Z power transmission					●								●		●	●
Z-to-X/Y power transmission				●	●								●		●	
Z-axis rotary motor					●								●			
Z-axis linear motor														●		
Gap-spanning unit										●		●				
Overhang support unit											●	●				
Reinforcement for 2 adjacent units						●		●	●		●					
Reinforcement for 2+ adjacent units							●									

Figure 3.61. Functionality matrix for the component set used in the Moses self-replicating construction machine. (courtesy of Matt Moses[915])

Moses' self-replicating construction machine (Figure 3.62) is a 3-axis Cartesian manipulator made only from parts in the previously described component set that can assemble a wide variety of devices, including duplicates of itself. The machine is kinematically capable of grasping, manipulating, and placing all of the components required for constructing its own duplicate, including the hardware required to manipulate mechanical components but excluding the portion responsible for control. The constructor lacks any type of sensor or onboard control and so must be controlled either by a human operator or a sophisticated external controller. Construction activities include the retrieval of components from a storage site and their subsequent connection to an assembly or operating plane, but components must initially arrive at the storage site through the action of another entity — namely, a human operator. Moses[915] lists the entire sequence of 410 steps (specific operations) that must be executed by the construction machine in order to install each of the 45 parts in its replica, in proper order, proceeding from (A) to (D) in Figure 3.62.

In the actual hardware implementation (Figure 3.63), constructor movements were sequenced by a human operator controlling the manipulator through a switch box. Moses candidly admits that "the idea did not work as well in reality as it did in simulation. In order to make a functioning constructor, some of the problems had to be solved by cheating — gluing certain parts together, for example. So the constructor and the device it constructs are not entirely identical. In many cases, the constructor could not develop

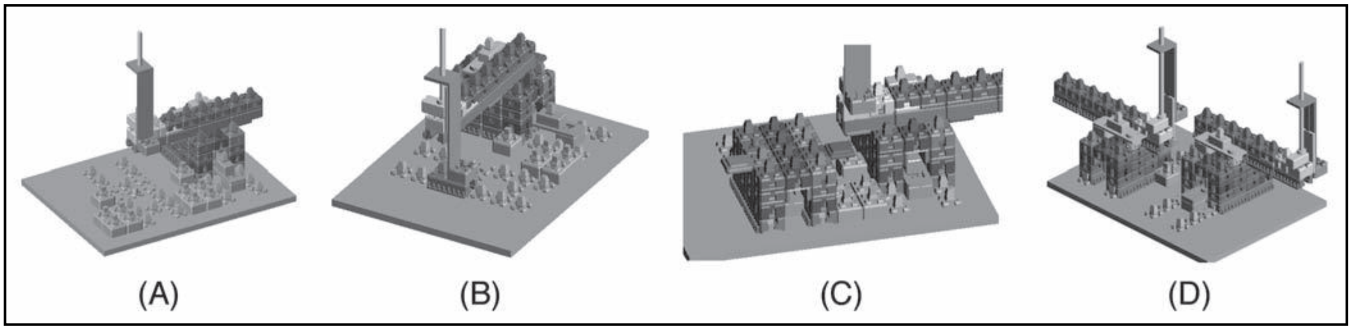


Figure 3.62. Moses' self-replicating construction machine. (A) The constructor prior to replication. (B) The constructor lays down "Part #1" of the replica. (C) The base platform is completed. (D) The constructor completes its replica. (For clarity, the storage site for the 45 parts of the duplicate machine is omitted). (courtesy of Matt Moses[915])

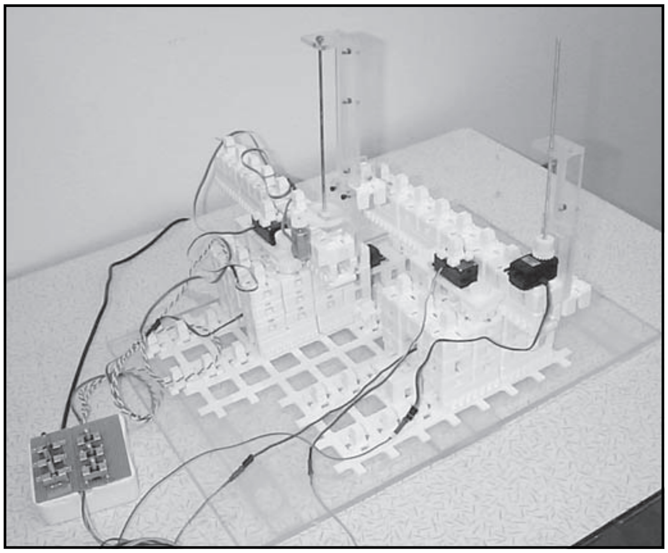


Figure 3.63. Actual physical implementation of Moses' self-replicating construction machine. (courtesy of Matt Moses[915])

the necessary force to assemble components. The necessity of strengthening the constructor with methods outside of the allowed fastening techniques can be eliminated in future iterations by producing parts of higher tolerance, revising the part set, or revising the constructor design. Problems with the boom could also be solved by revising the design of the constructor. A gantry-crane manipulator, where the boom is supported at each end, would avoid deflection problems and allow accurate placement of parts. Gantry-cranes are usually wrapped around their workspace, being larger than what they work on. This makes designing a gantry crane that can assemble a duplicate of itself difficult. The problem of running wires to the motors can be solved by laying conductive traces on the plastic parts.... While, kinematically, the design was capable of accessing and connecting the necessary parts to assemble a duplicate of itself, lack of stiffness due to the design of both components and manipulator prevented it from assembling its duplicate in reality." Nevertheless, after an assisted replication both devices were operable.

3.19 Self-Replicating Robots for Space Solar Power (2000)

A 3-day NSF/NASA workshop[18] was held in Arlington, Virginia in April 2000 to identify fundamental and applied research issues associated with manufacturing and construction of very large systems in space, especially systems designed to convert and deliver massive amounts of solar energy to the Earth's power grids from either Earth orbit or the Moon. The manufacture and assembly of such systems, as well as the production of photovoltaic cells, major structures, transmission subsystems, and robotic facilities from lunar materials will probably require the use of large numbers of semi-autonomous yet cooperating robots. Reminiscent of the 1979 Telefactors Working Group of the NASA New Directions Workshop (Section 3.13), this new NSF/NASA Workshop generated no new replicator designs but acknowledged that if "means were found to make the manufacturing robots partially or mostly self-replicating, the amount of material brought from Earth for such manufacturing could be greatly reduced." The Workshop produced a detailed R&D funding recommendation* for research on self-replication totaling $8.2 million.[19] Workshop participants were told that a lunar power system[1007,1008] might require only about 5,000 robots — not so many that self-replication is absolutely necessary, but certainly a large enough number to require new research in "teleautonomy."

The Workshop[18] identified three principal enabling robotics technology areas common to all space solar power (SSP) generation scenarios, the first two being:

In-situ production of robot parts. "This area involves the automated manufacture, assembly and repair of robot parts and subassemblies, a first step towards making a self-replicating robot…At some point it will become highly desirable to have the machines be able to reproduce themselves. Self-replicating robots will greatly lower the required launch mass to produce an SSP generator. The same technology that is needed to manufacture in-situ parts for the generator should eventually lead to the in-situ production of robot parts and robots."

Large numbers of cooperating robots. "This area involves the capability of having multiple robots cooperate in completing a task that cannot readily be done by a single robot. Research is needed in both groups of heterogeneous and homogenous robots. Space solar power systems will involve large numbers of robots (tens of thousands) all of which must act in a semi-coordinated fashion…Lunar production systems can be teleoperated/supervised from Earth. As materials extraction, fabrication, and assembly processes become more complex, the autonomous robotic systems should provide greater efficiencies."

Workshop participants further concluded: "Potential self-replication designs can support the space solar power (SSP) objectives in at least three ways: lowered construction costs, lowered

---

** Research recommendations on self-replicating systems for lunar manufacturing with funding estimates by the NSF/NASA workshop[19] included the following:*

1. *Define system-level measures of effectiveness and models which couple the effect of alternative technologies and designs to investment costs and total system effectiveness; ~$0.2M*
2. *Develop a simulation capability with sufficient detail to determine manufacturing flow networks which are both transitive and intransitive and permit the determination of such parameters as closure, investment costs, production amplification and the degree of autonomy from human involvement; ~$0.5M.*
3. *Employing the simulation capability in item 2, examine a robotic hierarchical society which involves the natural extrapolations of self and mutual diagnostics, self and mutual repair, parts replacement from spares provisioning, parts replacement from scavenged parts of failed robots, and the construction of entirely new robots — including the reconfiguration of healthy robots — to serve emerging needs. The sea of parts available in the construction vicinity — although a long "bill of materials" — should enable a far longer list of possible robot species. Since this concept is not autotrophic it will not be completely self-replicating, but it should substantially increase the total system reliability and flexibility; ~$1M.*
4. *Employing the simulation capability in item 2, define the entire process from the mining of available raw material to the finished useful product, including the robotic society. Assuming that the "genome" of the robots will be under full human control, examine alternative approaches to accomplish replication closure: how are the robotic subsystems manufactured and how are their parent machines manufactured, etc. Determine producer/product cost and mass ratios and alternative investment costs for each level of closure. Estimate the optimum level of self-replication investment to maximize mission levels of effectiveness; ~$2M*
5. *Repeat item 4, except that varying degrees of autonomy — or internalization — of the robotic genomes shall be considered; ~$3M.*
6. *Migrate the understanding of self-replication attained by the past few decades of research on cellular automata to the understanding of the kinematic model; ~$0.2M*
7. *Continue to mine von Neumann's intellectual heritage through scholarly reviews of his work on the general theory of automata, complexity, reliability of large systems with unreliable components, and evolution; ~$0.1M*
8. *Examine additional biological and "super-biological" analogies which may benefit the mission, including epigenesis (growth and development), immune systems, learning, Lamarkian evolution (passing on acquired characteristics to progeny), language acquisition and reconfigurability; ~$0.2M*
9. *Encourage the molecular nanotechnology community to accelerate their research into universal constructors useful to the mission; ~$1M*

transportation costs by using extraterrestrial material and, most significantly, acceleration of the pace of space development so that humanity can benefit from space power over a time frame of decades rather than centuries."

A lunar power system proposed in the 1990s by Criswell[1007,1008] at the Lunar and Planetary Institute would require antipodal arrays of photovoltaic solar collectors with microwave transmitter panels on the lunar surface to be constructed from lunar raw materials using a local mining, processing, and manufacturing infrastructure with assembly and maintenance to be provided by "von Neumann machines"* (i.e., bootstrapping or self-replicating systems). An evaluation by Boeing engineers[1161] of five approaches to space solar power found that Criswell's proposal "has the highest costs and difficulty, but also has the highest potential to supply a significant part of the world's energy over the long term." A partially self-replicating (energy closure only; Section 5.6) lunar-based solar cell factory proposed in 1998 by Ignatiev et al[981] would be "a mobile, lightweight rover equipped with a series of solar concentrators for the volatilization and deposition of regolith-extracted elemental materials....The lunar solar cell production facility would be highly mechanized and remote controlled occupying about 4 m^3 at a mass of 300-400 kg. This compares extremely favorably to the current production mass of about 650 kg for 75 kW of silicon solar panels. It would require ~300 W-hr of electrical energy to grow 25W of solar cells, and hence would have an energy payback time of 10-12 hrs. This makes the in-situ lunar solar cell fabrication technique essentially self-generating in that the cells grown would after 10-12 hr generate excess energy that could be used to grow more cells.

3.20 Three-Dimensional Solid Printing (2000-present)

The GOLEM (Genetically Organized Lifelike Electro Mechanics) Project[927-930] at Brandeis University, and related earlier efforts in "evolutionary robotics,"** [584-593] are an attempt to extend evolutionary techniques into the physical world by evolving diverse electro-mechanical machines (robots) that can be manufactured by automated fabrication,[1162,1163] personal factories,[999] stereolithography (using a UV laser to selectively cure a photopolymerized resin),[1111] solid freeform fabrication (SFF),[997,998,1126] selective laser sintering (SLS) and laser direct metal deposition (DMD),[1164,1165] laminated object modeling (LOM) and fused deposition modeling (FDM),[933-935] or rapid prototyping (RP).[1110-1121] Lipson and Pollack of the Volen Center for Complex Systems at Brandeis University describe a set of preliminary experiments evolving purely electromechanical systems composed of thermoplastic, linear actuators and "neurons" (evolved artificial neural network) for the task of locomotion, first in simulation and then in reality. Lipson used the FDM technology of Stratasys Inc. which is based on feeding a thermoplastic feedstock wire into a heated nozzle, then positioning the nozzle to deposit the plastic to build a part layer by layer. After 3-D solid printing, these simulation-evolved systems then faithfully reiterate*** the performance of their virtual ancestors.

Lipson and Pollack start with a set of elementary building blocks (bars, actuators and neurons), and a set of operations that can join building blocks together, take them apart, or modify their dimensions. The first task to be optimized was the speed of locomotion. Virtual robots are initialized empty, each with zero bars, zero actuators and zero neurons. The computer applies design operations to the robots at random. After each operation is carried out, the computer measures the performance of the robot in a simulator. If it is better than average performance (speed, in this case), the computer makes more of it, and if it is less than average, the computer removes it. The computer continues to run all day. In the beginning, most of the virtual robots are just piles of random building blocks and their performance is zero. By chance, after, say, a hundred generations, a particular group of building blocks happens to assemble in such a way that something moves a little. That accidental assembly is then replicated because it has above-average performance.

Figure 3.64. 3D Systems' ThermoJet 3-D printer allows CAD designers to quickly print a 3-dimensional model to 50-100 micron resolution.[932] (courtesy of 3D Systems)

After many more generations, but essentially the same kind of progress steps, Lipson and Pollack observe the emergence of robots that look like they were designed, but really are just the outcome of this simulated natural selection.[474-476] The robots are rendered into real physical models using a 3-D printing process (Figure 3.64) that prints solid objects voxel by voxel (though with some multivoxel overlap due to imperfect materials flow) using a raster scan motif, and these robots function largely as expected when built (Figure 3.65). This work demonstrates a complete physical evolution cycle, wherein a robotic system can design and manufacture new robots, but it is not yet self-replication because the machines produced are not as capable as their precursors and the robots require the rather substantial intervention of a 3-D printer machine and human assembly assistance (typically including actuators, power sources and electronic controls) in order to complete their physical instantiation.

Earlier work by Chocron and Bidaud[1167] attempted to use a genetic algorithm to evolve both the morphology and inverse kinematics of a modular manipulator composed of prismatic and revolute joints, but their simple serial construction approach precluded

---

** See related footnote, Section 3.11.*

*** In evolutionary robotics,[593] "an initial population of artificial chromosomes, each encoding the control system of a robot, is randomly created and put into the environment. Each robot is then free to act (move, look around, manipulate) according to its genetically specified controller while its performance on various tasks is automatically evaluated. The fittest robots then "reproduce" by swapping parts of their genetic material with small random mutations. The process is repeated until the "birth" of a robot that satisfies the performance criteria."*

**** Evan Malone[1166] reports that the performance of the physical machines was typically less impressive than, although qualitatively similar to, the simulations.*

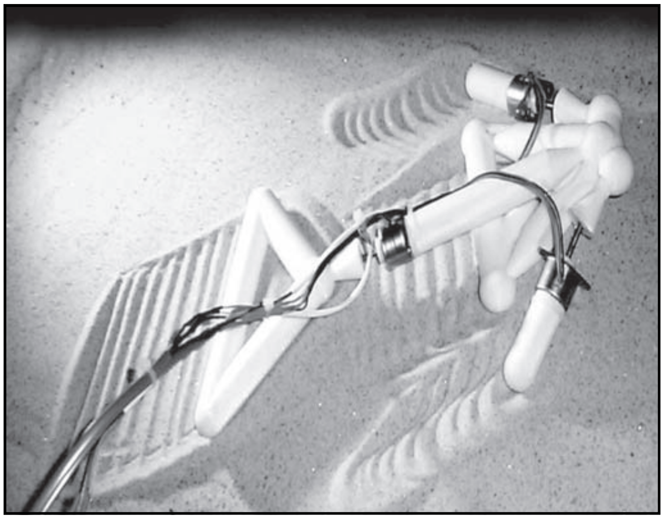


Figure 3.65. GOLEM Project[928] uses robotic system to automatically design and manufacture new robots; a computer-designed, 3-D printed robot crawler is shown below. (courtesy of Hod Lipson and Jordan Pollack)

the spontaneous emergence of unforeseen or novel solutions. Similarly, Dittrich et al[1168] described a "random morphology robot" which is an arbitrary 2-D structure composed of links and motors; the controller is evolved, then manual changes are applied to the robot to test its behavior with an impaired or mutated body.

Lipson and Pollack point out that they are a long way from making a 3-D printer that can print another 3-D printer, as would be required for full self-replication.* They used the cheapest available technology, a 3-D printer that melts plastic and prints it in layers. Instead of their cheap $50,000 "fab," they note that they could have used a $2M or a $10M "fab" that would build bigger devices out of stronger material. But Sony Corp. reportedly already uses a robot "fab" for most small consumer electronics. Stereolithography and rapid prototyping[1110-1119] enjoy widespread artistic,[1169] academic** and commercial interest,[931,934] and machines which can print mechanical, electrical, and electronic logic componentry together on a small scale*** are under development.[1170]

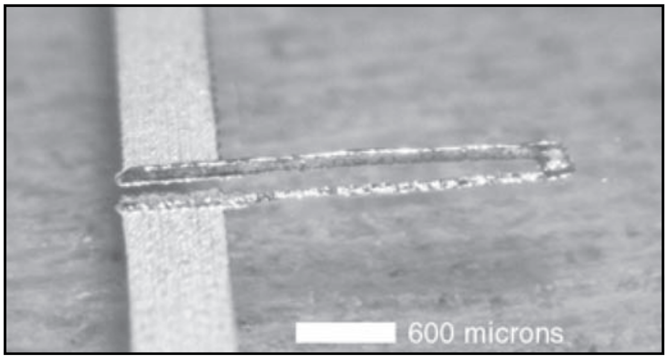


Figure 3.66. An inkjet printed thermal actuator. (courtesy of MIT Media Lab)[1177,1186]

For example, by 2000, Stephen C. Danforth at Rutgers University was printing 3-D electronic components from ceramic materials that can be insulating, semiconducting, or fully conducting, depending on their exact composition.[933] This allowed printing of 3-D electromechanical components such as sensors and actuators with feature sizes as small as 200 microns, which Danforth's group hoped to halve by 2003. By 2002, Joseph Jacobson's group at the MIT Media Lab had printed working inorganic field-effect transistors,**** [1175] radio frequency identification tags,[1176] and working three-dimensional machines such as linear drive motors and thermal actuators[1177] with feature sizes of ~100 microns (Figure 3.66) by laying down hundreds of layers of nanoparticle-based inks using an inkjet printing technique that requires no clean room and temperatures under 300 °C. Several other research groups at Lucent's Bell Labs and Cambridge University (U.K.) have also printed transistors using organic polymers,[1176] and there is a growing literature on the ink-jet printing of electronic components.[1178-1184] One rumor had it that Hewlett-Packard is planning to sell a personal desktop 3-D printer for as little as $1000.[1185]

According to John Canny,[1187,1188] head of the "flexonics" team at the University of California at Berkeley: "Flexonics could be called macroscopic MEMS, or polymer mechatronics. Our goal is to design fully-functional appliances and human-interfaces from organic materials, and to build them without assembly using 3-D printing techniques." Team members are developing a vocabulary of passive

---

** In 1998, C. Phoenix[1171] informally sketched out a design for a macroscale kinematic replicator a few cubic feet in volume that would use two hydraulic-powered manipulator arms to machine, then assemble, its own components out of a soft plastic feedstock which would then be ultraviolet-cured to yield hard plastic parts, analogous to the stereolithography system offered by Vicale Corp.[934] The acoustically-powered plastic replicator, composed of perhaps ~2000 parts, would be controlled by an onboard 8086-class computer built from cured-plastic fluidic logic elements including 1 KB of RAM, receiving instructions from a 1400-foot long strip of hole-punched control tape. Most details such as specific materials and assembly procedures, basic closure issues, process error rates, and accessibility of required machining tolerances were not explicitly addressed.*

In 2003-2004 graduate student Mike Collins,[1172] working in the Mechanical Engineering program at the University of Florida, set as his Masters thesis objective "to build a piece of hardware that can take amorphous raw material and draw on an unconstrained amount of energy to build a copy of itself and any tools that it used to make that copy. I am using Rapid Prototyping Machinery to build component parts and specialized equipment for mass manufacturing. My aim is to focus on the mechanics and logistics of such a system. This project will be aided by the following simplifying factors: 0% energy closure, limited materials to be refined, and large initial material store allowed (yolk subassemblies); the project will be hindered by the following complicating factors: limited materials from which to design parts and subassemblies, and high information closure (90% target)."

*** Saul Griffith[1173] in Jacobson's group at MIT built a working printer capable of printing in chocolate and beeswax with the LEGO® toolkit — using a simple extrusion chamber based on a worm screw and three-axis actuation based on the LEGO® robotics motors and the LOGO programming platform. "A three dimensional printer using programming languages designed for children and low cost consumables has been implemented. One can imagine a new paradigm for children's toys involving the child in the design, production, and then eating! of their own play-things."[1173]*

**** Griffith[1173] notes that Dow Chemical has a system[1174] for "printing" large buildings. "A reaction vessel for the polymerization and foaming of polystyrene is placed at the end of a beam that rotates around a central pole. By extruding a bead of foam as the beam rotates and moves up the pole a dome is created. These domes have been used to make medical clinics, and as emergency relief shelters after earthquakes in Nicaragua."[1173] In a similar development, Behrokh Khoshnevis at the University of Southern California has created a "contour crafter" robot that will "print" houses using a computer-guided nozzle (riding on a movable overhead gantry) that squirts successive layers of concrete on top of one another, shaped by side-trowels mounted on the nozzle, to build up vertical walls and domed roofs; the first one-story 2000 square foot house is expected to be built in 2005.[2335]*

***** In December 2000, Jacobson was quoted[1176] as confidently predicting: "We should be able to demonstrate a very simple processor in the next 12 to 18 months. Our goal is to follow the trajectory silicon took, and start printing processors with perhaps several hundred transistors, moving to thousands and then more." Making Pentium-like chips on a desktop fab is "likely a several-year research project, but we believe it's doable."*

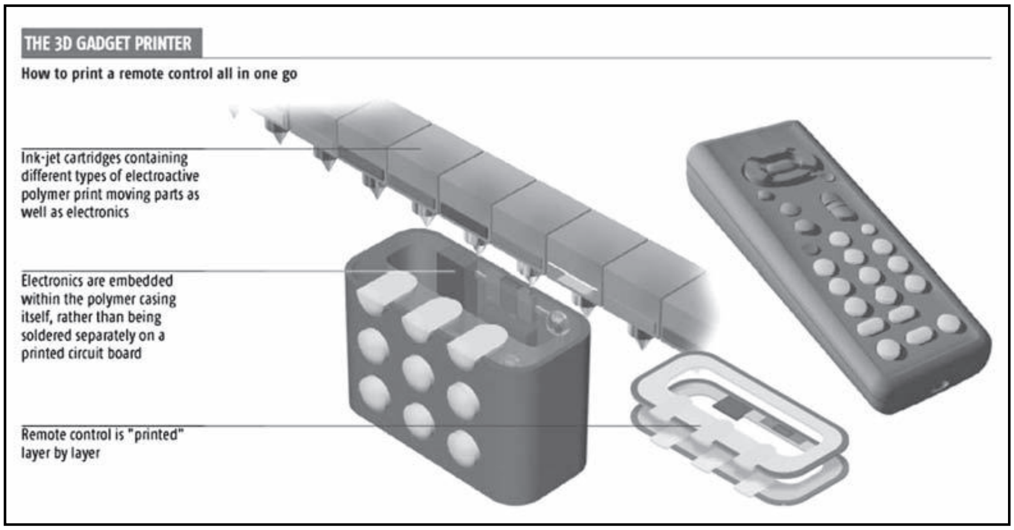

THE 3D GADGET PRINTER
How to print a remote control all in one go
Ink-jet cartridges containing different types of electroactive polymer print moving parts as well as electronics
Electronics are embedded within the polymer casing itself, rather than being soldered separately on a printed circuit board
Remote control is "printed" layer by layer

Figure 3.67. The 3-D gadget printer. (courtesy of John Canny and New Scientist[1189])

and active mechanical components including flexure, hinge, and rotary joints. Instead of creating an appliance casing and then laboriously filling it with electronic circuit boards, components and switches, says one report,[1189] flexonics will allow printing a complete and fully assembled device by setting down layer upon layer of conducting and semiconducting polymers in such a way that the required circuitry is built up as part of the bodywork (Figure 3.67). "When the technique is perfected, devices such as light bulbs, radios, remote controls, mobile phones and toys will be spat out as individual fully functional systems without expensive and labor-intensive production on an assembly line." The Berkeley team has already worked out how to print electronic components such as transistors, capacitors, inductive coils and other semiconductor components.[1189] Says Jeremy Risner,[1190] a member of Canny's team: "My background is bioengineering and I'd like to develop models based on living designs...Maybe a rather flat insect with wriggling limbs and some actuators." Risner hopes to develop a fully functional, mechanical and electronic device by the end of 2004, using several printer heads to lay circuits, transistors, capacitors, sensors and casing — all printed by one machine in one run, using a multitude of print heads patterning each material in layers.[1190] Thin-film printing of electronic devices is already a reality.[1191]

The Thermojet Solid Object Printer[932] manufactured by 3D Systems uses inkjet technology to print solid objects to ~85 micron resolution in X, ~60 microns in Y and ~40 micron resolution in Z. According to the product literature, printer volume is 2.57856 m^3 and model build time is ~10^4 sec with a maximum model size of 0.0095 m^3, hence the time to build a printer's volume worth of models is ~2.7×10^6 sec, or ~1 month "replication" time for a 499 kg printer.

The Z406 system built by Z Corporation in cooperation with Hewlett-Packard offers color inkjet-like 3-D solid printing technology to ~76 micron resolution in Z, with a vertical build speed of 152 microns/minute across a square 203 mm x 254 mm build area, up to a maximum object height of 203 mm.[1192] (The product literature gives printer volume as 0.902496 m^3 and model build speed as 1.31×10^{-7} m^3/sec, so the build time for a printer volume is 6.9×10^6 sec, or ~3 months "replication" time for a 210 kg printer.) Each of the three exterior dimensions of Z Corp.'s smallest solid printer unit, the Z400, are still much larger (740 mm x 910 mm x 1070 mm) than any of the build volume dimensions.[1192] Standardization of 3-D descriptive data formats is already under discussion.[1193]

Smay, Cesarano and Lewis[1194] at the University of Illinois and Sandia Labs use an ink jet printer to deposit colloidal inks carrying tiny particles made of metals, ceramics, plastics, or other materials in a layer-by-layer sequence to directly write desired 3-D patterns with 100 micron features. The robotic deposition or "robocasting" gel must be thick enough to support itself as it spans empty spaces, and must also retain its shape without significant shrinking or sagging as it hardens.

There is already a vast literature[1195] on microstereolithography,[1196-1221] with applications including microactuators,[1222,1223] microbiomedical devices,[1224,1225] microelectronics,[1226] microelectrophoretics,[1227] microfluidics,[1228,1229] microoptics,[1230] micropumps,[1231-1233] and microrobots,[1234] and electrodeposition microfabrication or EFAB™ is well-known.[1122-1124] Gas phase SFF (Solid Freeform Fabrication) has also been investigated[1125-1127] — laser beams passing through acetylene gas produce solid carbon rods.[1235] In this manner Westberg et al[1236] have fabricated a 3-turn boron spring 2 mm high and 200 µm wide; Maxwell et al[1237] have formed micro-solenoids and micro-springs from C, W, and TiC fibers as small as 5 µm with horizontal deposition rates >12 cm/sec for high-pressure (11 atm) deposition; and layered microwall[1238] and ~300-µm diameter column[1239] structures have also been manufactured.

Progress is being made in solid printing at even smaller size scales.[1240-1245] For example, in 2001 Satoshi Katawa and colleagues at Osaka University[1240] used two-photon micropolymerization in resin to create a 2 micron x 10 micron 3-D sculpture of a bull (Figure 3.68) to a voxel resolution of 120 nm. In the single-beam geometry, a single high numerical aperture objective lens is used to tightly focus the laser light so that two-photon processes are confined to the focal volume — the two-photon absorption cross-section for known materials is quite small, so that the light intensity outside the focal volume is insufficient to launch these reactions, permitting 3-D resolution in a single-beam laser scanning system. The researchers chose the shape of a bull because it has "a very sophisticated 3-D shape with sharp tips and a smooth and rough body," noted Hong-Bo Sun, a team member who says that the same technique might also be used to manufacture microscopic sensors and 3-D computer memories.[1246] Marder and Perry[1247] at Georgia Tech, also using two-photon 3-D lithography with a two-photon resist, have made 3-D structures of silver, gold, and copper metal as small as 0.170 micron wide and 0.500 micron long, with linear writing speeds up to 100 cm/sec. They believe their process can produce feature sizes as small as 100 nm.

Many other approaches have been tried. Riehn et al[1248] used near-field optical lithography (a scanning near-field optical microscope (NSOM/SNOM) with a UV laser) to fabricate functional 2-D patterns with 160-nm feature sizes from the conjugated polymer

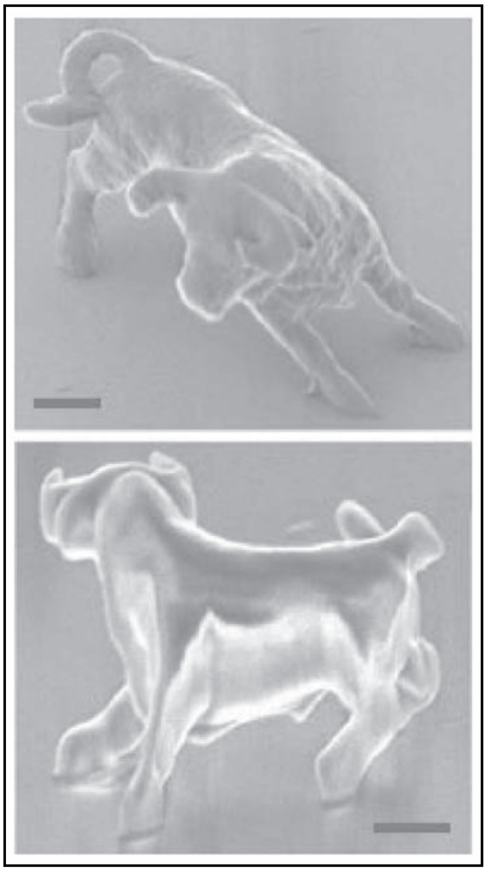


Figure 3.68. A 3-D resin-sculpted bull the size of a red blood cell. (2 μm scale bars; photo courtesy of S. Kawata et al[1240] and Osaka University)

poly(p-phenylene vinylene). Stuke's group[1249-1251] has generated 3-D microstructures by rapid laser prototyping, and 3-D nanostructure fabrication via focused-ion-beam CVD is described in Section 4.7. Wilson, Boland, and Mironov et al[1241-1244] have printed 3-D tubes of living tissue using modified desktop printers filled with suspensions of micron-sized cells instead of ink — a first step towards printing protein patterns, complex tissues, or even entire organs. Similarly, Vaidyanathan and Mulligan[1252] are solid-printing resorbable implantable bone scaffolds for surgeons, as is the company Therics.[1253] Sciperio Inc.[1254] is developing a "direct-write tissue deposition apparatus" for the "creation of engineered tissues, or neo-organs" composed of "vascularized 3-D tissue scaffolds and living cells." Mirkin's group[2809] has created dip-pen nanolithography arrays that can write 2-D nanoscopic patterns layer by layer on surfaces — a minimum linewidth of 60 nm has been demonstrated using an eight-pen microfabricated probe array. Proteins can be printed with an AFM-based "nanofountainpen".[1255] Alexandridis and Docoslis[1256] have used electrophoresis to stack latex, silica or graphite microparticles into 3-D structures of prescribed size and composition, held together by the electrical field, and it is claimed that the same process could be applied to nanoparticles. Saul Griffith[1173] in Jacobson's group has described tabletop "personal fabricators" and several tools for the rapid prototyping of micron-scale feature-sized devices for the manufacture of printed microelectromechanical systems (PEMS). This would include laser-based stereolithography using a rapidly (up to ~4 KHz) switched micromirror array to achieve highly parallel operation.[1173] Says Neil Gershenfeld,[1257] head of the MIT Center for Bits and Atoms: "We're approaching being able to make one machine that can make any machine. I have a student working on this project who can graduate when his thesis walks out of the printer, meaning that he can output the document along with the functionality for it to get up and walk away."

Lipson and Pollack say that while they are contemplating the conditions necessary for full electromechanical self-replication, this is not a primary goal of their research: "Self-replication is very easy in software and cellular automata. What is harder is to find the 'bootstrap.' Just as a forge, a mill, and a lathe lead to more mills and lathes, and ultimately to the industrial revolution, and just as understanding stored program computers and digital communications lead to all of modern computer science and the internet, our set of robotic technologies could someday lead to a self-sustaining 'bootstrap' and to more complex robotically-designed and robotically-constructed robots." Adds Rodney Brooks,[1258] director of the Computer Science and Artificial Intelligence Laboratory at the Massachusetts Institute of Technology, on the Lipson-Pollack work: "This is a long-awaited and necessary step towards the ultimate dream of self-reproducing machines."

3.21 Bererton Self-Repairing Robots (2000-2004)

Curt Bererton, in early 2004 a Ph.D. candidate at Carnegie Mellon University, is investigating the design and potential utility of robots capable of self repair or cooperative repair.[1259-1262] Research issues include: (1) What are some general design rules for repairable robots? (2) How can we quantify the performance of different robot teams? (3) What is the best way to achieve cooperation in a team of robots? (4) Is there a principled way in which multi-robot planning can be achieved? Bererton is most interested in self-sustaining systems — that is, systems that can operate in the absence of humans for extended periods of time — and in creating robots that can truly repair each other and exist as a self-sustaining robot colony. Figure 3.69 is a "concept picture" showing examples of useful capabilities in such a colony reminiscent of several "replicating lunar factory" proposals (e.g., Sections 3.13, 3.24, 3.25 and 3.29). Many of these capabilities — including "constructing a new robot" or (at least partial) self-replication — would also be useful in applications other than space missions.

Bererton believes that "robots will become an integral part of human society much like computers are today. To reduce the amount of down time in robotic factories, mines, and robot activity in general, robots should and will repair other robots," saving time and money, and keeping critical infrastructure well maintained. "Clearly, many of these activities won't be seen on commercial robots for some time. It will begin with self-diagnostics that pinpoint malfunctioning components for a human repair technician. A great example of this kind of technology can be seen in modern printer/photocopying machines which indicate the location and repair procedure for stuck paper faults, open doors, lack of toner, and many other kinds of errors. One of the first capabilities I expect to see is for robots to be able to tow each other reliably to either an automated repair facility or to a capable human repair technician."

Bererton has designed and built two simple robots (Figure 3.70) which are capable of mutual repair,[1260-1262] in which all of the electrical modules can be swapped out using a forklift type mechanism. These robots, the first of their kind ever built,[1261] worked well; videos are available online.[1263]

These robots exhibit several key capabilities required for a repairable robot team, including fault detection, diagnosis, and repair steps. The design concentrates on maximal re-use of existing components by having robots repair each other. Notes Bererton:[1259] "The construction of these robots proved a point. When I began my research on repairable robots I encountered much skepticism

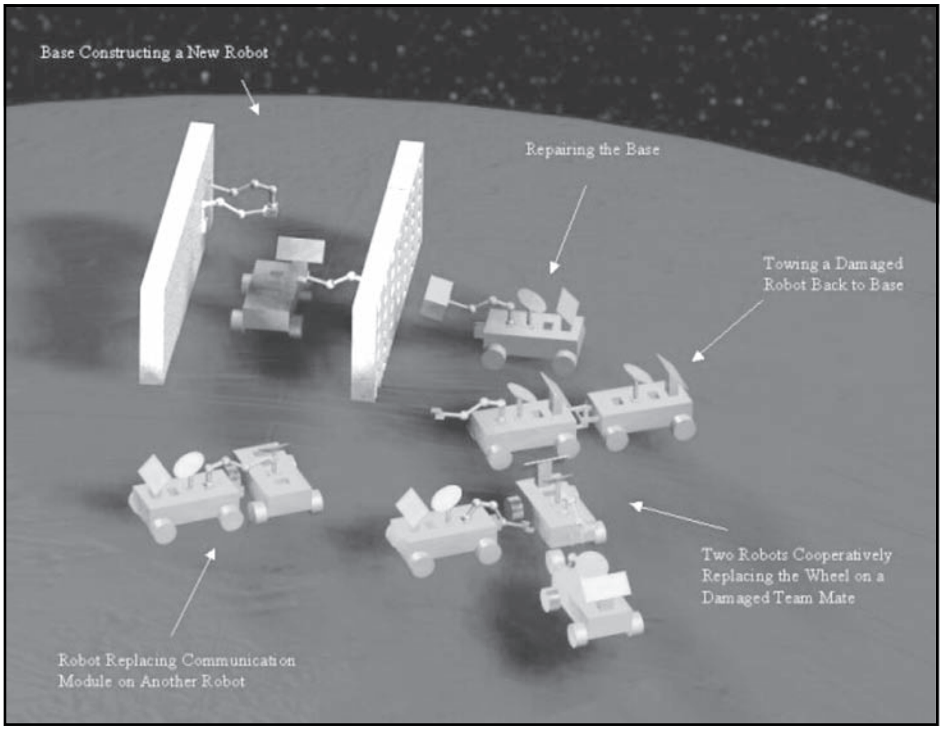

Base Constructing a New Robot
Repairing the Base
Towing a Damaged Robot Back to Base
Two Robots Cooperatively Replacing the Wheel on a Damaged Team Mate
Robot Replacing Communication Module on Another Robot

Figure 3.69. Self-sustaining system of mobile robots. (image courtesy of Curt Bererton[1259])

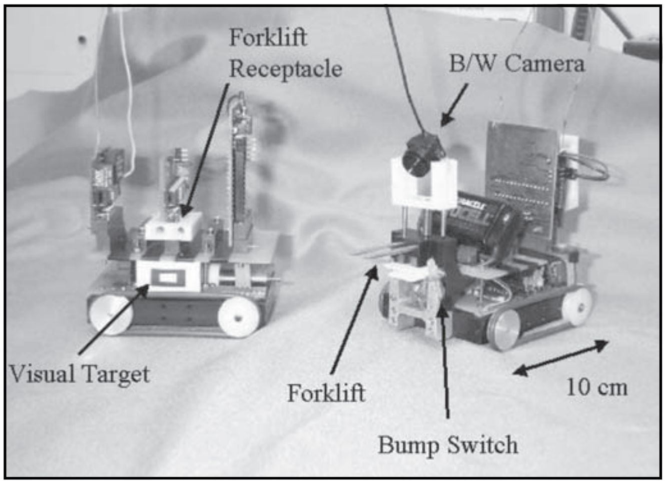


Figure 3.70. Robots capable of mutual repair. (image courtesy of Curt Bererton[1259])

regarding whether or not robots with cooperative repair capabilities could ever be created. With these robots I demonstrated that such capabilities were not only possible, but that they could be achieved using technology available at the time [and] that repairable robots aren't as far away as some would believe."

3.22 Brooks Living Machines Program (2001-present)

Rodney Brooks is both the Director of the MIT Computer Science and Artificial Intelligence Laboratory (CSAIL) and the Chairman and CTO of iRobot, a 120-person robotics company. Well known for his pioneering work[1264-1269] in making small, simple workable robots using the subsumption architecture (e.g., Attila[1270,1271] and Genghis[1271,1272]) and later for his investigations of basic learning processes in humanoid robots (e.g., Cog[1268,1273] and Kismet[1268,1274]), in 2001 Brooks began an entirely new research program[1275] called "Living Machines" — moving away from building humanoid robots to considering instead the differences between living matter and non-living matter.[1276] "At one level we're trying to build robots that have properties of living systems that robots haven't had before," he explained in a June 2002 interview.[1277] "We're trying to build robots that can repair themselves, that can reproduce (although we're a long way from self-reproduction), that have metabolism, and that have to go out and seek energy to maintain themselves."

Brooks is very interested in replicating systems:[1277] "We're also trying to build self-reproducing robots. We've been doing experiments with Fischer Technik and LEGO®. We're trying to build a robot out of LEGO® which can put together a copy of itself with LEGO® pieces. Obviously you need motors and some little computational units, but the big question is to determine what the fixed points in mechanical space are to create objects that can manipulate components of themselves and construct themselves. There is a deep mathematical question to get at there, and for now we're using these off-the-shelf technologies to explore that. Ultimately we expect we're going to get to some other generalized set of components which have lots and lots of ways of cooperatively being put together, and hope that we can get them to be able to manipulate themselves. You can do this computationally in simulation very easily, but in the real world the mechanical properties matter. What is that self-reflective point of mechanical systems? Biomolecules as a system have gotten together and are able to do that." The specific projects being studied in Brooks' lab are in a constant state of flux, but the following are a few examples of some efforts that were being pursued in early 2003.

One of Brooks' graduate students, Jessica Banks,[1278] was directly investigating the biological mechanisms of reproduction from a kinematic cellular automaton (Section 3.8) approach, using LEGO® parts as the primitive building blocks. According to her original research plan: "The immediate goal is to build a robot that joins together the same pieces out of which it is built. To simplify this problem, we chose to construct the robot out of a limited set of LEGO® parts analogous to nature's atomic building blocks: carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorous. The robot is designed to assemble these blocks by combining minimal sensing and actuation with the passive incorporation of the environment in which it is situated. As such, we are hoping to draw an analogy between the robotic system and that of molecule structures which organize due to the energy flow of and reactions with the liquid water medium in which they are suspended. The future goal is to try to answer questions about whether it is possible for machines to beget machines. We would like a robot to autonomously assemble copies of itself, either directly or through a sequence of intermediate robotic constructions. What does reproduction mean for a robot and what is required for this process? Can we extract a fixed point for robotic self-assembly that we can apply to other inorganic and organic systems?"

Another graduate student, Lijin Aryananda,[1279] was pursuing a slightly different approach: "We seek to explore the ambitious question of how to construct self-replicating non-trivial robots. In nature, we observed that evolution first generated self-replicating single-celled organisms. Multicellular organisms didn't appear in abundance until approximately 550 million years ago, during the Cambrian explosion. Based on this observation, we propose to divide our target problem into two parts: how to construct self-replicating simple robots and how these units may aggregate to form self-replicating non-trivial robots. In this project, we plan to carry out various computational experiments to study the following issues: how do unicellular aggregates form and under what conditions are they more beneficial? Why do individuals in aggregates surrender their ability to reproduce? How does a unicellular organism's self-reproducing mechanism evolve to the self-reproducing mechanism in multicelled organisms? How does differentiation emerge in multicellular organisms? Our hope is that the answers to these questions can be ultimately applied in designing complex robots that self-replicate."

A postdoc in Brooks' lab, Martin C. Martin,[1280] was pursuing an evolutionary approach to self-replicating machines more akin to the work of Lipson and Pollack (Section 3.20): "Evolved bodies will be constrained to use parts typical of machines, such as rigid cylinders, metallic plates and electric motors. Existing rigid body simulators are well suited to this task. The world will be much richer than existing work, containing areas of water, land and air, as well as varied terrain in each area. Later, other variations may be added, such as day/night cycles and tides. Previous work has largely focused on neural networks as the representation for brains, but an alternate representation could lead to behaviors of a much greater complexity. Reinforcement learning will be used to allow the creatures to adapt to their environment, with the details of the learning framework under genetic control. This will allow the complexity of the robot to mirror the complexity of the world, rather than forcing that complexity to be present in the genome. It will also allow the brain to better adapt to changes in the body due to mutation. This will allow more mutations to be explored, ideally allow evolution to be more efficient. A success in this work could provide a new way to design machines of a greater complexity than is possible at the moment. Successful creatures could be reverse engineered to determine how they work. This could lead to insights into the proper method of combining development and learning, possibly providing new paradigms for traditional hand-designed machines. The work could also point the way to giving important properties of living systems to machines, and shed light on the nature of those qualities."

3.23 Chirikjian Group Self-Replicating Robots (2001-2003)

Chirikjian's group in the Department of Mechanical Engineering at Johns Hopkins University (JHU) has progressed beyond earlier work[1281-1283] on self-reconfiguring systems (Section 3.8) and now is one of the first laboratories in the world to pursue an active experimental research program on macroscale kinematic self-replicating robots. Gregory Chirikjian and Jackrit Suthakorn, a graduate student in Chirikjian's group, offer a simple operational definition[1284-1286] of the subject of their inquiry: "Self-replication is the process of assembling a functional robot from passive components. The robot that is assembled (the replica) is an exact copy of the robot doing the assembling." Suthakorn, Chirikjian and his undergraduate students appear to have built and operated the world's first mobile LEGO®-based self-replicating machines.[1287]

3.23.1 Prototype 1 (2001)

As recorded in his April 2003 Ph.D. thesis, Suthakorn[1287] built his first simple prototype remote-controlled LEGO®-based robot in 2001 to demonstrate that it is mechanically feasible for a robot to produce a copy of itself. "Prototype 1" consisted of 7 subsystems: left motor, right motor, left wheel, right wheel, micro-controller receiver, manipulator wrist, and passive gripper (Figure 3.71(A)). Several passive fixtures were located in the assembly area to assist the robot in assembling its replica. The robot depends for its success on these external passive fixtures, which are not actuated but are manipulated by the replicator robot. The original robot is remotely controlled to relocate its subsystems from a storage area to the assembly area, whereupon the original robot is guided to perform the assembly process (Figure 3.71(B)) — a process Suthakorn[1287] describes as follows:

"The original robot retrieves the left motor subsystem from the storage area and slides it into a motor assembling fixture (this fixture is designed to have a narrow slot so that when the motors are placed in it, they are forced to align with each other). The robot then moves the right motor subsystem from the storage area into the motor-assembling fixture. After both left and right motors are aligned in the fixture, the robot exerts pressure on the subsystems so that they snap together and form one piece. The original robot then manipulates the motor-assembling fixture so as to release the motor subsystem, which completes the first stage of assembling the subsystems. The robot then takes the motor subsystem and slides it into a wheel-assembling fixture which is designed to assist attaching the left and right wheels to the subsystem. After the wheels are successfully attached to the motor subsystem, the robot manipulates the wheel fixture to release the assembled part. The robot continues to perform procedures similar to the previous steps to relocate parts and assemble them. This process leads to the completion of a replica (Figure 3.71(C)) of the original robot."

3.23.2 Remote-Controlled Self-Replicating Robots (2002)

Chirikjian and Suthakorn[1284-1290] next describe several prototypes of self-replicating robotic systems that were developed by the undergraduate students and graduate student Yu Zhou during a one-semester mechatronics course taught in the Spring of 2002 at JHU. The students were divided into eight groups to explore designs and implementations of the concept of self-replicating robotic systems. The goal of the course was for each group of students to design a robot with the ability to create an exact functioning replica of itself, starting from a complete set of components or subsystems. A set of rules was established to motivate students to minimize the complexity of each individual subsystem while maximizing the number of subsystems in their designs. The use of LEGO® Mindstorm kits and additional LEGO® parts reduced building time in order to allow students to invest more time in designing and testing the prototypes, and the robots were remote-controlled (teleoperated) rather than autonomous so students could focus on the mechanical issues involved in the design of self-replicating systems. All experiments were conducted in an arena made of wood sheets 1 m^2 in area with walls 30 cm high. The four most distinctive prototypes for self-replicating robotic systems included:

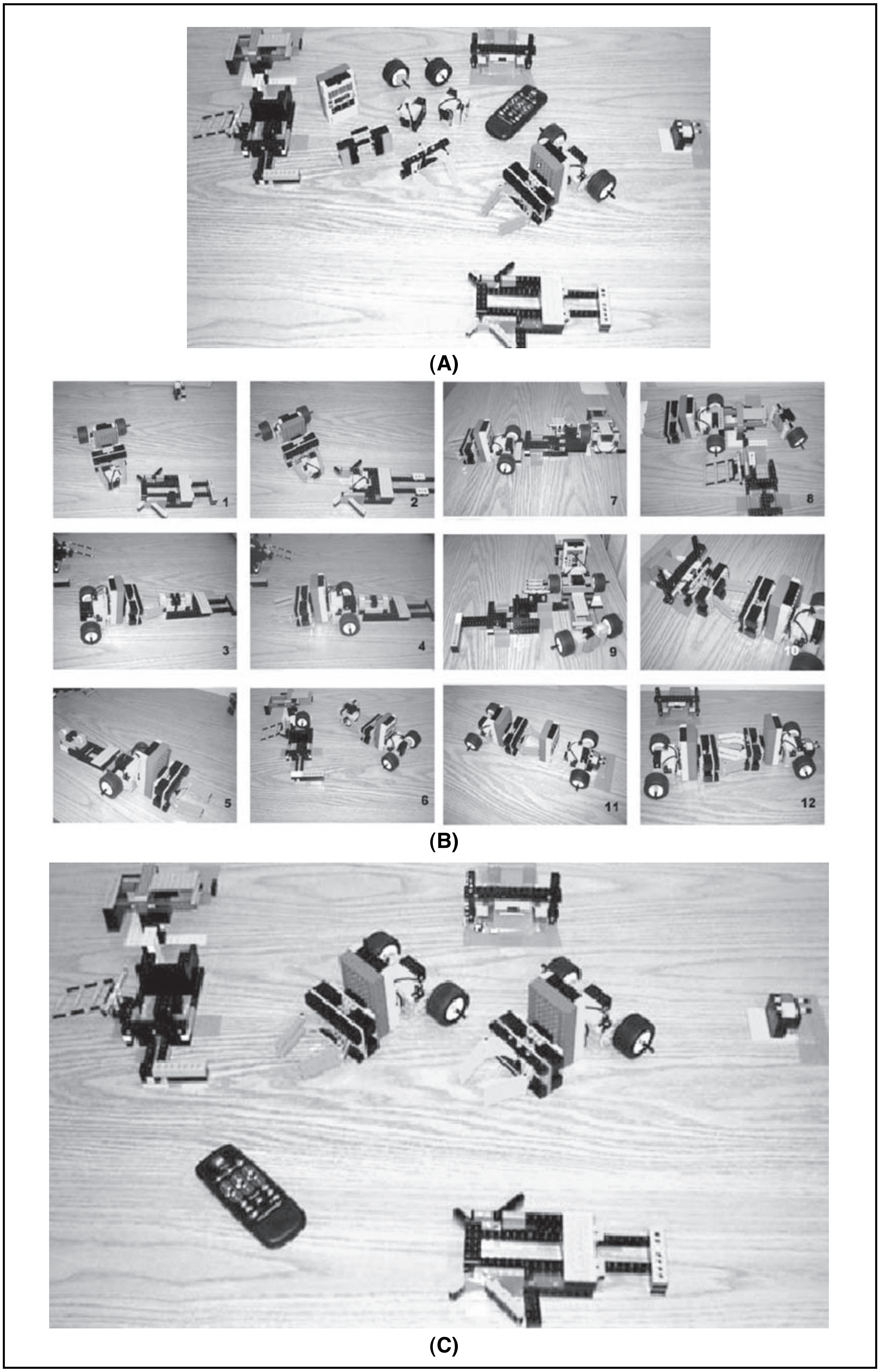


Figure 3.71. LEGO®-based teleoperated kinematic replicator: Prototype 1. (A) Prototype 1, an unassembled set of the replica's components, and environmental fixtures. (B) Prototype 1 undergoes self-replication via teleoperation and external fixtures. (C) Prototype 1 and its completed replica. (courtesy of Jackrit Suthakorn and Gregory Chirikjian, Johns Hopkins University[1287])

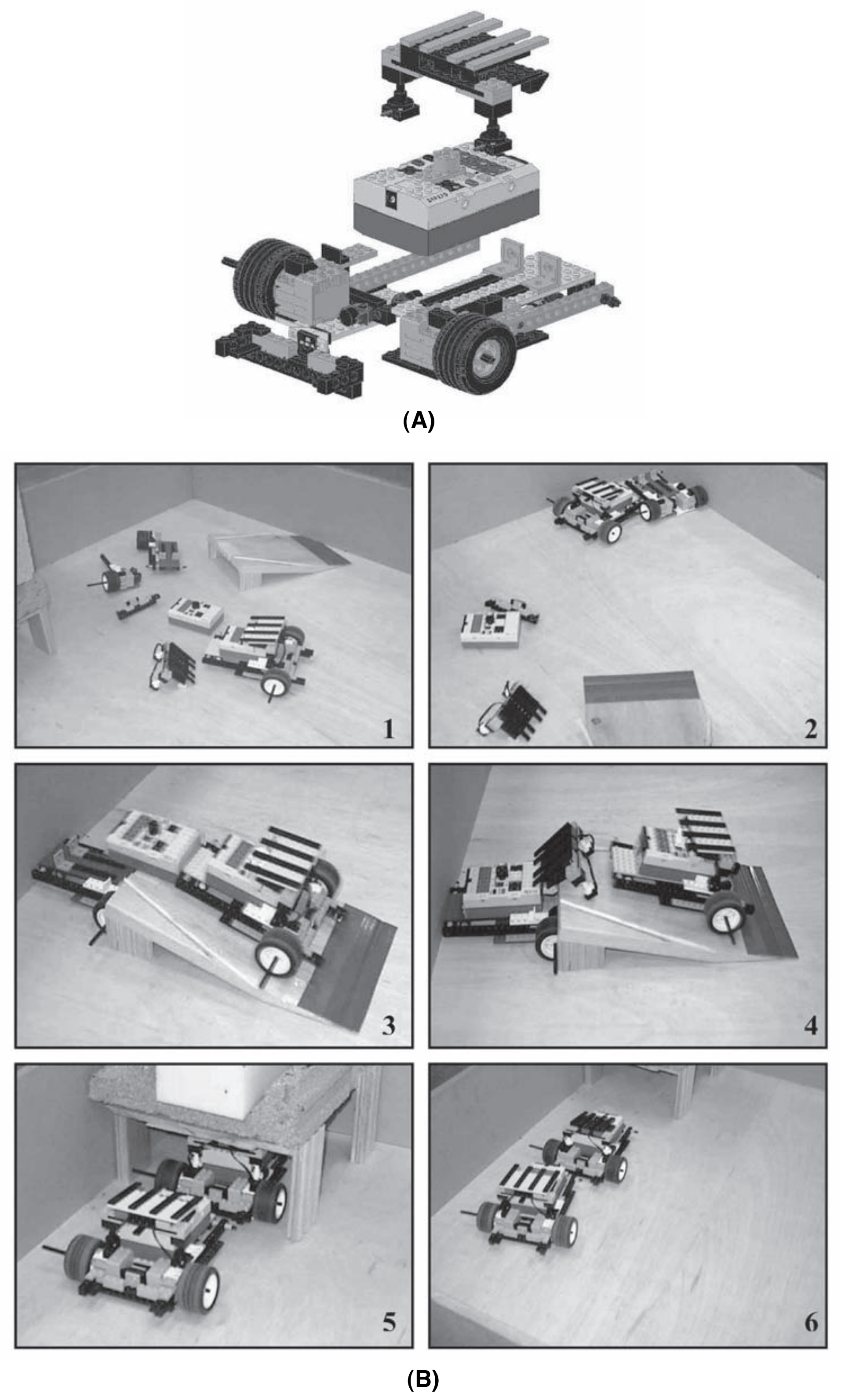


Figure 3.72. LEGO®-based teleoperated kinematic replicator: Robot 1 (courtesy of Chirikjian group, Johns Hopkins University).[1285] (A) Exploded view of Robot 1. Student design team: Jim Bankard, Oprema Ganesan, Oleg Gerovichev, Masaya Kitagawa. Teaching Assistants: Jackrit Suthakorn, Yu Zhou. (B) Self-replicating process of Robot 1. The process begins with the original robot dragging the right part (which consists of half of the chassis, the right wheel and the right motor) to a wall. Then the left part (which consists of half of the chassis, the left wheel and the left motor) is pushed to connect with this right part. The left and right parts of the replica are securely merged by adding the bumper which has interlocks to both subsystems. The combined subsystems are moved and oriented to a desired position and orientation next to the ramp. The original robot then pushes the controller up to the ramp, and gently drops and inserts the controller on the top of the previous combination of subsystems. Note that the ramp has a constrained shape to force both controller and connector to be in their places. The connector is fixed in its place in the same fashion. The last step is to physically force the connector to be in contact with the controller by pushing the replica in the tunnel-like area with a wedge on the ceiling. This will force the connector to be in place. After pushing the replica several times, the electronic connectors on the replica finally make contact. The replica is able to operate in the same way as the original does.

Robot 1: Fixture-Based Design. The first example consists of five subsystems (left part, right part, bumper, controller, and connector). Two fixtures are used: a ramp with a constrained shape which is fitted to the controller and the connector; and a tunnel-like cave with an attached wedge on the ceiling used to physically force the connector in place (Figure 3.72).

Robot 2: Single-Robot-Without-Fixture Design. Robot 2 has five subsystems (left wheel system, right wheel system, left cradle, right cradle, and controller). The original robot has a pair of prongs in the front part to manipulate components and the unfinished replica, and uses the rear part to push the subsystems to the wall in order to compress the subsystems together (Figure 3.73).

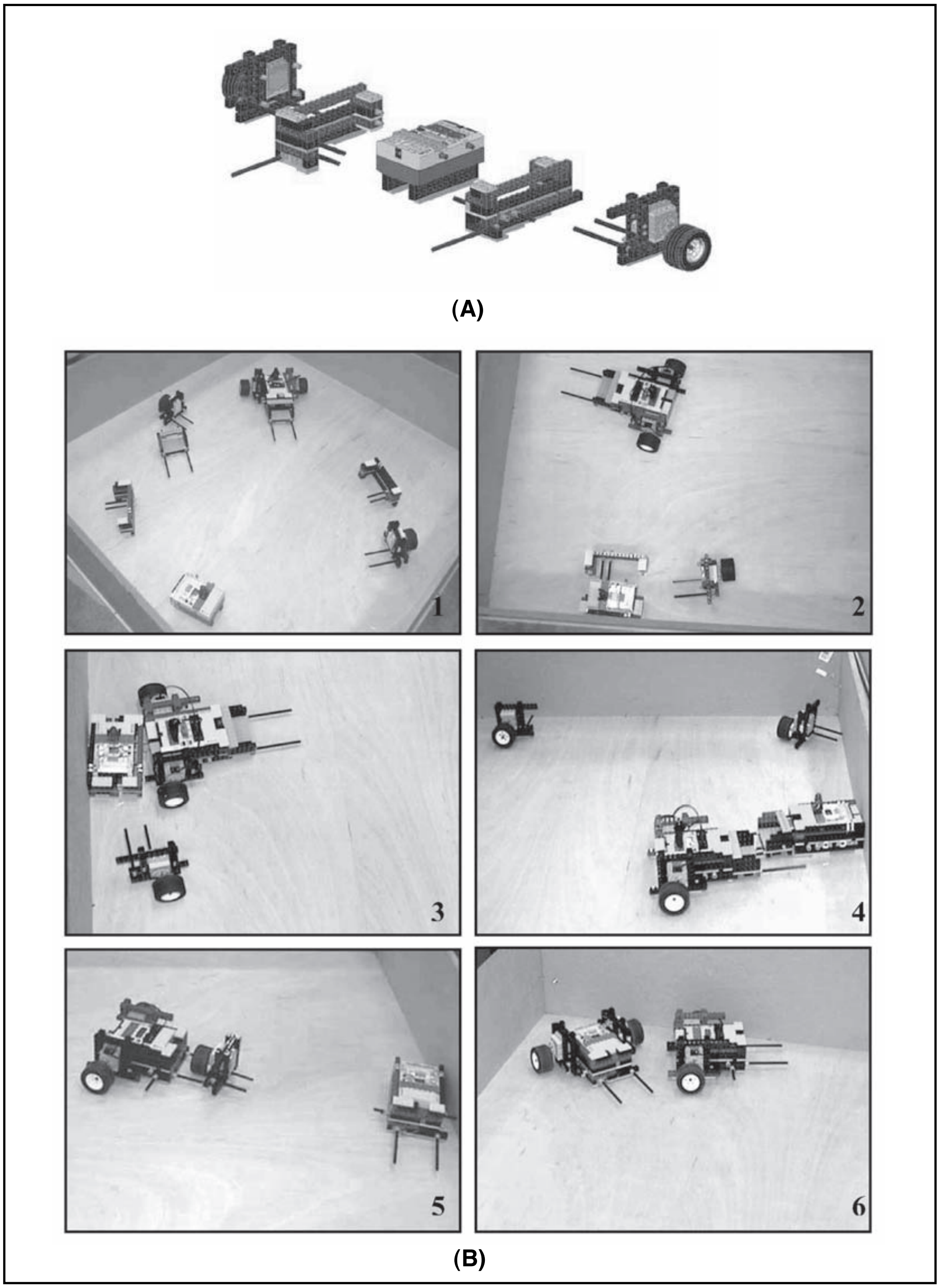


Figure 3.73. LEGO®-based teleoperated kinematic replicator: Robot 2 (courtesy of Chirikjian group, Johns Hopkins University).[1285] (A) Exploded view of Robot 2. Student design team: Tabish Mustafa, Omar Rivera, Mark Sorensen, Brian Weineler. Teaching Assistants: Jackrit Suthakorn, Yu Zhou. (B) Self-replicating process of Robot 2. The process begins with the original using its prongs to move the controller to a wall. Then the robot brings one side of the cradles to insert into the slot under the controller, and pushes both parts to the wall. The first two subsystems are then connected. The other cradle is combined with the previously combined subsystems in the same way. The left and right wheel systems are then manipulated, and combined to the previously connected subsystems in a similar fashion. The replica is then able to operate.

Robot 3: Another Fixture-Based Design. This robot consists of three subsystems: the controller; the drive system; and the cage. The cage has a hinge that allows the top part of the cage to open and close to cover the wheel system and controller. The electronic connectors are attached on the top part of the cage. A passive dual linkage is hanging to assist in opening the cage (Figure 3.74).

Robot 4: Operating Subsystems Assist in the Replication Process. In this design a subsystem is able to operate before finishing the replication process, and hence can assist in the assembly of the complete replica. Robot 4 (Figure 3.75) consists of the controller, the left thread (a long wire with electronic connectors), the right thread, and the gripper subsystem.

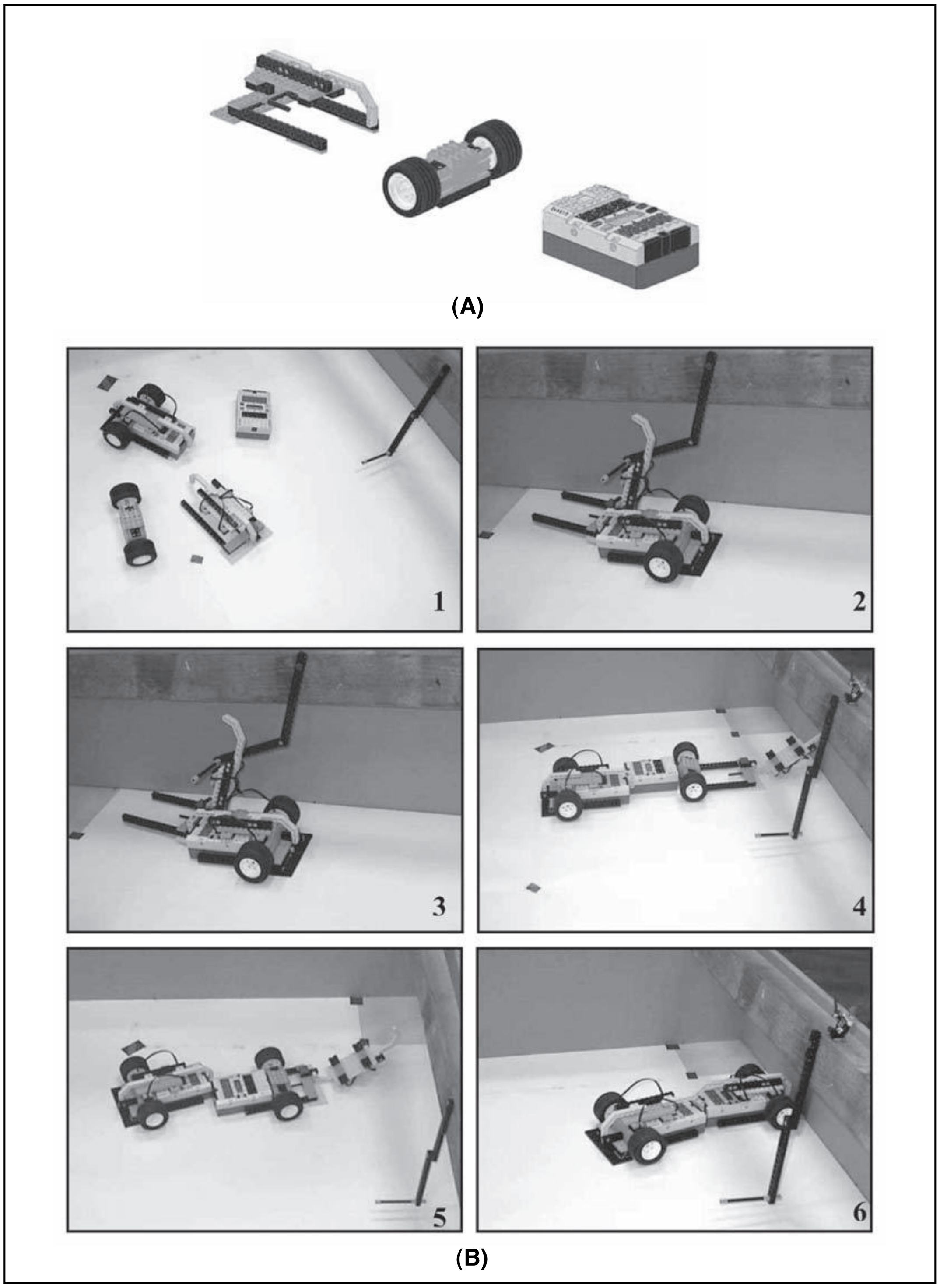


Figure 3.74. LEGO®-based teleoperated kinematic replicator: Robot 3 (courtesy of Chirikjian group, Johns Hopkins University).[1285] (A) Exploded view of Robot 3. Student design team: James Del Monaco, Paul Stemniski, Sten-Ove Tullbery, Jason Wachs, Chris Wong. Teaching Assistants: Jackrit Suthakorn, Yu Zhou. (B) Self-replicating process of Robot 3. The process begins with the original robot pushing the cage to hook with the passive linkage, and then the top part of the cage is opened. The original robot then inserts the drive system and controller into the cage, respectively. The combined but unlocked subsystems are pushed to the wall. Because of the design of the top part of the cage, which is a curved shape, the original robot pushes the cage and the other two subsystems to the wall, and the cage is automatically closed. The replica is then completed.

The authors[1285] concluded: "The study of self-replicating robots is an interesting research area which has not been extensively pursued in recent years. A number of self-replicating robot designs were presented here. The different designs devised by our students has helped us to identify new research problems, and to categorize self-replicating robots. Many challenging issues remain. Our future work will be to develop truly autonomous[1291] (rather than remote-controlled) self-replicating robots."

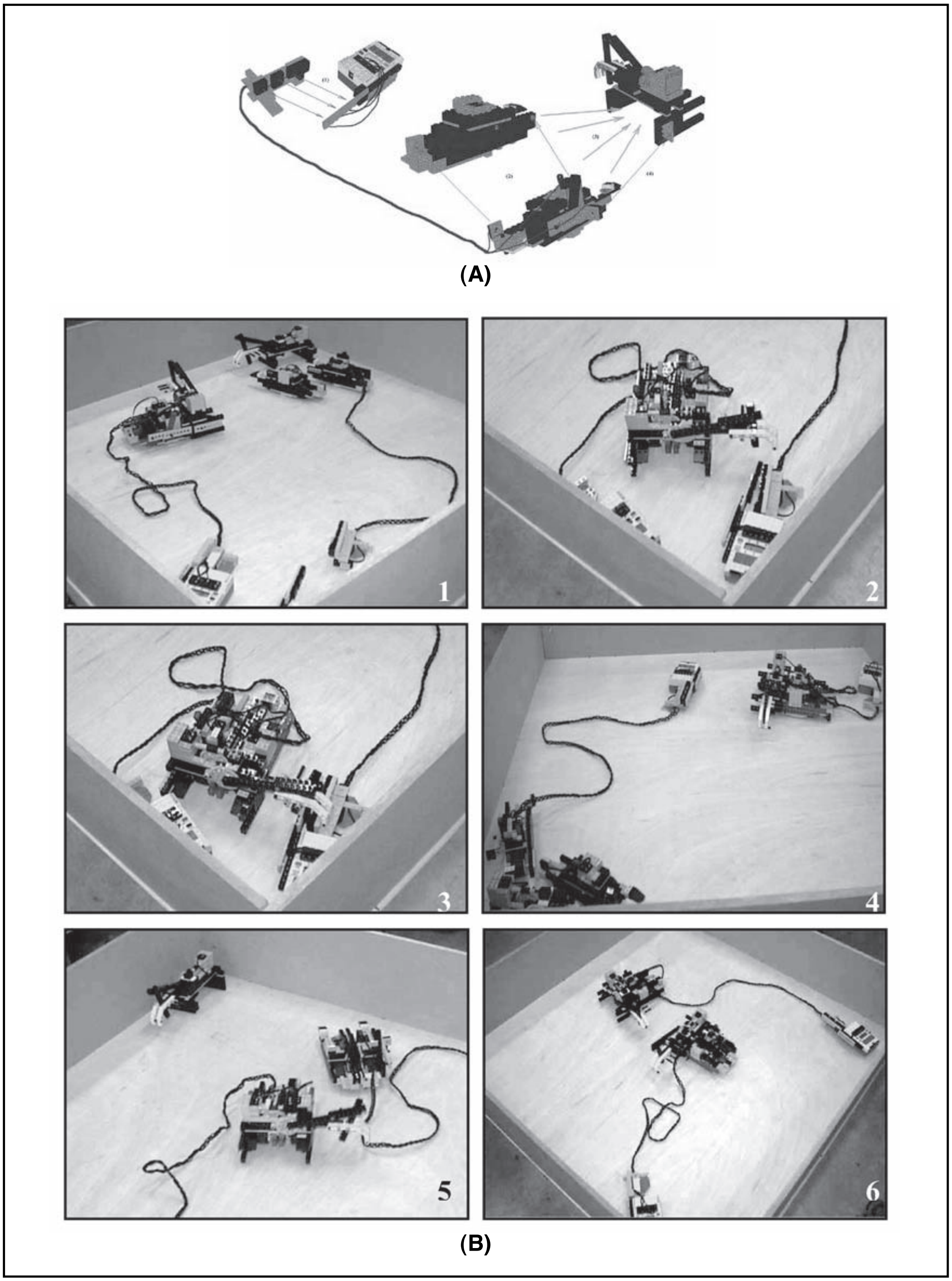


Figure 3.75. LEGO®-based teleoperated kinematic replicator: Robot 4 (courtesy of Chirikjian group, Johns Hopkins University).[1285] (A) Exploded view of Robot 4. Student design team: Jonathan Lim, Tak Liong, Daniel Moon, Jon Tang, Vincent Wu. Teaching Assistants: Jackrit Suthakorn, Yu Zhou. (B) Self-replicating process of Robot 4. The process begins when the original robot uses the gripper to carry the electronic connector (attached to the long wire) to the side of the controller. Then, the original robot uses the gripper to grasp and join the electronic connector to the controller. Once finished joining the electronic connector, the left thread, connected to the end of the wire, is now functioning. A human user is now able to control this subsystem. The original robot still continues moving subsystems next to each other for the next steps. The functioning subsystem is controlled to move to a convenient location for combining other subsystems. Once the left and right threads are aligned, the original robot uses the gripper to compress and join their connectors. The gripper subsystem is a big part. From its structure the gripper is able to slide to the top of the combined left and right threads after the functioning threads are driven into a side of the gripper subsystem. Then, the original robot helps tightening the connectors. The replica is now in a fully stable and operational status.

3.23.3 Semi-Autonomous Self-Replicating Robot (2002)

Following the Spring 2002 mechatronics course experiments (Section 3.23.2), Suthakorn's third project was to design and build a self-replicating system in the manner of a robotic factory.[1287,1288] The system consisted of an original robot, subsystems of three fixed-position assembly stations (the factory), and finally a set of complex parts from which replicas of the original robot are assembled. By following painted lines on a 3.75 meter x 3 meter work surface, the robot could move autonomously from station to station along the lines without any human guidance, while still being remotely controlled at each station by a human operator, hence the system is aptly described as semi-autonomous. Feedback sensors were incorporated in each assembly station to automatically activate their functions.

The author gives an explicit step-by-step replication procedure for the "robot factory".[1287] At Station 1 (Chassis Assembly), there is an 8-step procedure; at Station 2 (Motor and Track Assembly), a 12-step procedure; and at Station 3 (Gripper Assembly), a 4-step operational procedure, e.g.,:

1. Ascend backwards on the ramp.
2. Turn 180° on the top of the ramp and dock into position.
3. Operate lift down until gripper slides into the front of the original robot.
4. Descend backwards on the ramp.

The entire self-replication procedure "was conducted several times [and was] generally successful with some disparity of completion time (ranging from 45-75 minutes); however, there were some technical errors, such as battery failure." Several workcells were needed to assist the original robot in the replication process because the robot could not directly build its replicas. Each workcell served as a station in this factory-like replicating system, providing an example of an "indirectly replicating" robot (Section 5.1.8). An AVI video clip is available online.[1292]

3.23.4 Suthakorn-Cushing-Chirikjian Autonomous Replicator (2002-2003)

Suthakorn's fourth and final project presented here was to design and build a fully autonomous self-replicating robotic system.[1287,1289] This work took place under the direction of professor Gregory Chirikjian; also, Andrew Cushing, a local high school student, assisted in the building of the device. The robot and its replicas each consist of four separate complex parts or "subsystems": controller, left tread, right tread, and gripper/sensor components (Figure 3.76(A)). The prototype device used two light sensors to detect objects and track lines (blue-painted lines and silver spots) for navigation on the 2 meter x 3 meter work surface. Magnets and shape-constraining blocks helped to align and interlock the complex parts during replication (Figure 3.76(B)).

The replica's parts are prepositioned at known locations and the original robot starts at the initial position (Figure 3.76(C)). The explicit replication procedure is worth quoting verbatim from Suthakorn[1287] in its entirety:

1. The original robot starts following the line from the starting point to the first subsystem (the "right tread" complex part) using sensor No. 1.
2. Once light sensor No. 2 detects the first subsystem (right tread), the original robot stops and begins the grasping process, then grasps the right tread subsystem.
3. After the grippers are closed, the original robot will turn to the right until it detects a line.
4. The original robot will follow the second line until it reaches the assembling spot.
5. When light sensor No. 1 on the original robot detects the silver acrylic spot (the assembling spot), the robot will stop and begin the attaching process.
6. The original robot opens the grippers and gives a final push to secure the right tread subsystem (of the replica) to the controller subsystem (of the replica).
7. The original robot then backs up and turns to the left until it detects a line value on sensor No. 1.
8. The original robot follows the line until it reaches the left tread subsystem.
9. Once light sensor No. 2 detects the second subsystem, the robot will stop, and begin the grasping process by closing its gripper around the left tread's wedge.
10. The original robot turns right until it detects the next line.
11. The original robot will follow the second line until it reaches the assembling spot.
12. Once the original robot reaches the assembling spot, it begins the attaching process.
13. The original robot opens its gripper to release the left tread subsystem.
14. The original robot gives a final push on the left tread subsystem to help secure it.
15. The original robot then backs up and turns left until it detects the next line, using sensor No. 1.
16. The original robot follows the line to the final subsystem.
17. Once it reaches the gripper/sensor subsystem, it will stop and begin the grasping process.
18. The original robot closes its gripper and turns right until it detects a line value with sensor No. 1 (Figure 3.76(D)).
19. The gripper/sensor subsystem is now transferred to the assembling spot.
20. Once the original robot reaches the assembling spot it will stop and open the gripper.
21. The original robot backs up and turns left until sensor No. 1 is a line value.
22. The original robot then follows the line back to the starting point and is ready to replicate the next replica system.
23. The finished replica robot self-activates 20 seconds after completion and begins following the line to the starting point.
24. Once each robot reaches the starting point, it begins the replication procedure again.

Following this cookbook-like procedure, the original robot was capable of automatically assembling its replicas. The replication process took 135 seconds per cycle. While each of the four complex parts had to be placed in known locations, "the errors of positioning and orientation are not highly critical. We found slight errors during the grasping process in a few experiments (out of more than 20 trials) caused by improper placement of the subsystems. Overall, the system is robust and repeatable." An AVI video clip is available online.[1293]

In future work, Suthakorn planned "to build a self-replicating intelligence system[1290] such as a circuit controller and a mechanical decoder. This would fill the missing part of the self-replicating robotics research. However, our ultimate goal is to develop a

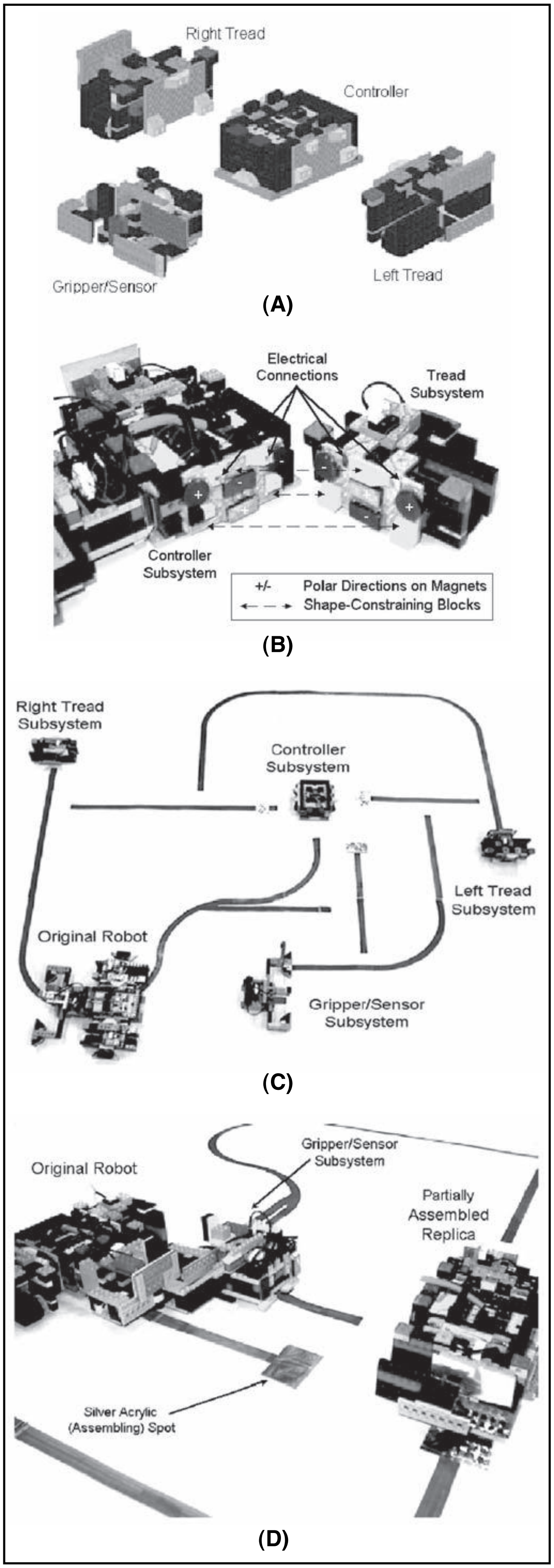


Figure 3.76. LEGO®-based fully-autonomous kinematic replicator. (A) Exploded view of the four complex components comprising the Suthakorn autonomous replicator. (B) Connections between controller and tread subsystems. (C) Layout of the experimental area. (D) Robot searches for the assembling spot while holding the replica's gripper/sensor part. (courtesy of Jackrit Suthakorn and Gregory Chirikjian, Johns Hopkins University[1287])

self-replicating robotic system capable of autonomously assembling its replicas from simple components using only electromechanical intelligence, i.e., a mechanical code and transistor-based control circuits. This eliminates complicated electronic components such as programmable micro-controllers, and makes the concept more appropriate for future space systems that can use in-situ resources for self-replication."[1287] Pursuing this objective, the syllabus for the Spring 2003 mechatronics course[30] at the JHU Department of Mechanical Engineering, called "the intelligence of self-replicating robots," is described as follows:

> *This course is a hands-on, interdisciplinary design project, in which juniors, seniors, and graduate students from all engineering disciplines work together to design, build, and debug robots. This year we continue the exploration of self-replicating robots. Last year, each group built a remote-controlled self-replicating robot. This year our goal is to build autonomous self-replicating electromechanical intelligences. Each group will build a robot consisting of an arm, a control circuit for the arm, and a machine code program to control the arm, among which the circuit and the code should be replicable. The objective is that the arm should be able to implement the same function as before, after being connected to the resulting new circuit and code. The whole system will be built by using LEGO kits. Students are required to build their own logic control circuits which are made up of LEGO pieces embedded with electronic components, such as transistors, resistors, and capacitors. The "program" will also be built with LEGO pieces, and should consist of at least 10 bits but not more than 100 bits. Presentation will be within the week from May 5 to 9, 2003.*

Interestingly, Suthakorn's autonomous replicator passed the "fertility test" recommended by the RSC Team of the 1980 NASA lunar replicator study[2] for their replication feasibility demonstration (Section 3.13.1): "All the replicas were also capable of completing the same replicating process," says Suthakorn.[1287] "We believe that this prototype was the world's first fully functional autonomous self-replicating robot."

3.24 Chirikjian Self-Replicating Lunar Factory Concept (2002)

Following in the tradition of the 1980 NASA study of self-replicating lunar factories (Section 3.13), Gregory Chirikjian et al[980] at Johns Hopkins University has further examined the utility and implementation of such missions, which could produce both energy and materials on the moon. Notes Chirikjian: "When self-replicating robotic factories take hold, the moon will be transformed into an industrial dynamo. The resulting refined materials and energy that will be produced on the moon will then provide capabilities for the exploration and colonization of space that could never exist otherwise. But the moon's resources cannot be exploited in a practical way by directly launching massive production facilities there. Hence, self-replicating systems are essential.

"In self-replicating systems, one or more functional robots assemble copies of themselves. The replicas may then act together as a swarm, or not. The [research] goal is modest: Design a simple self-replicating robot that (perhaps in collaboration with other robots of the same kind) will assemble a replica of itself from rigid components with geometric features that can be produced by casting molten material in a mold. While this method of component

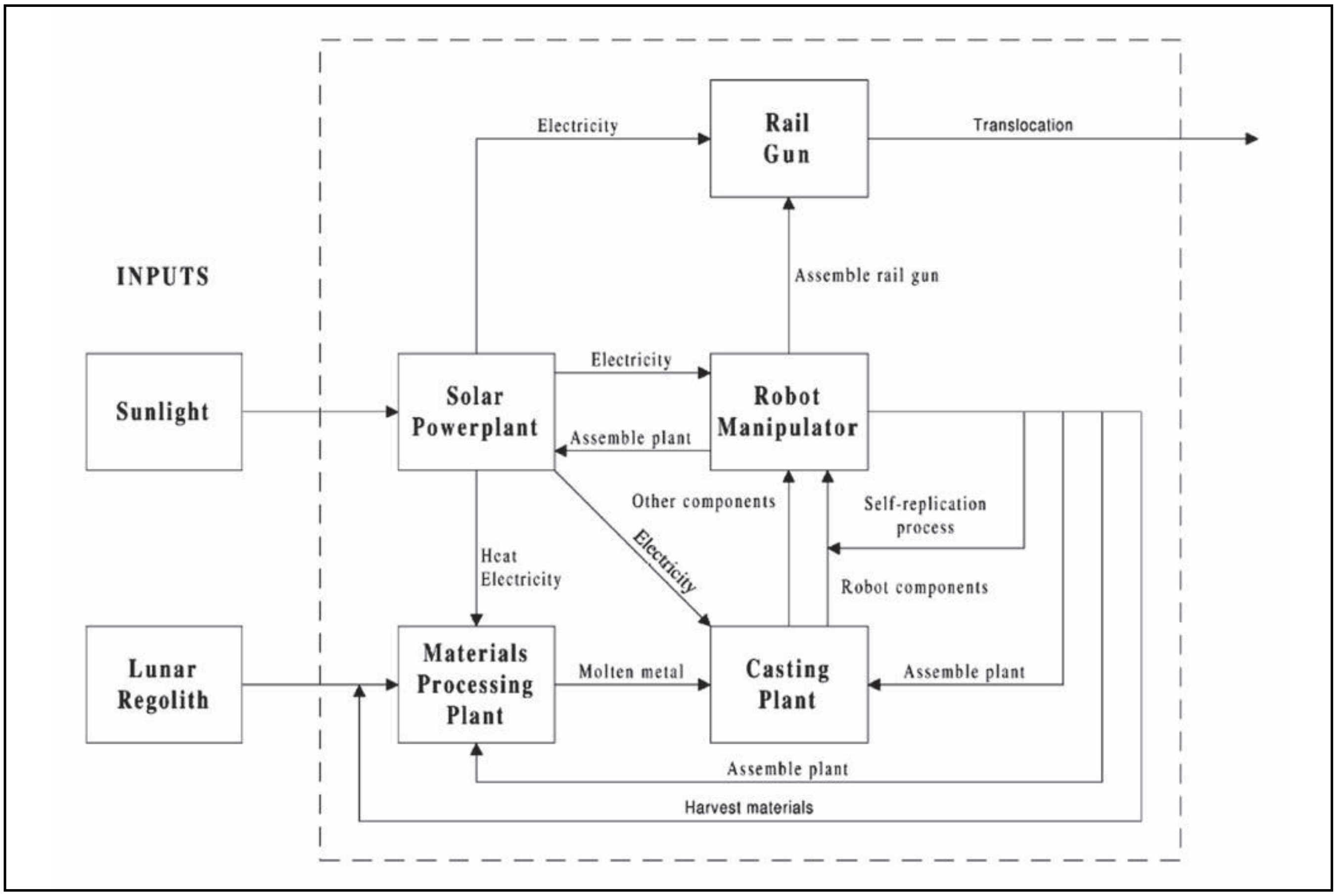


Figure 3.77. Architecture for self-replication. (courtesy of Chirikjian group,[980] © 2002 IEEE)

manufacturing is not the only one, it is easy to imagine that castings can be used to make new molds, and the new molds can in turn make new castings. Hence, this method of component production lends itself to overall system self-replication. In contrast, another manufacturing technique such as laser sintering could be imagined, but this would require the ability to reproduce a laser. No such need exists for casting." This is a departure from Freitas' NASA design (Section 3.13.2.2) which included both casting and laser sintering in the parts fabrication subsystem.

The overall architecture for Chirikjian's self-replicating lunar factory is shown in Figure 3.77; an artist's conception of the factory (Figure 3.78) is reminiscent of the earlier NASA work (Figure 3.49). There are four key subsystems in the Chirikjian lunar factory:[980]

1. **Multifunctional Robots**. These robots can assemble copies of themselves given a complete set of unassembled parts. Each robot may consist of a mobile platform as a base with attached manipulation devices, and will not only assemble replicas of themselves but also can be used to assemble the other three subsystems from their components. The addition of a suite of tool fixtures allows these robots also to be used for mining and local transportation of materials and components between subsystems within the ~1 km region of the lunar surface occupied by one factory site.
2. **Materials Refining and Casting Facility**. This subsystem takes in the strip-mined lunar regolith, melts it using power produced by the energy subsystem, and separates oxygen from the silicon, aluminum, and iron oxides that are plentiful in the regolith. These molten materials are then separated and fed into molds formed from sintered regolith. The resulting castings serve as components of new copies of all four subsystems.
3. **Solar Energy Conversion, Storage and Transmission**. The lunar factory uses both photovoltaic cells and solar radiation reflected and concentrated by mirrors. Photovoltaic cells power the robots, the rail gun subsystem, and also the electrolytic separation of elemental metals from oxides in the materials refining facility. Since the energy generated by one factory will be far in excess of the power requirements of the factory's own self replication needs, so the excess energy could be transmitted to low-earth-orbiting satellites using microwaves. Energy storage is provided by fuel cells assuming sufficient water or elemental hydrogen exists, or by other alternatives.

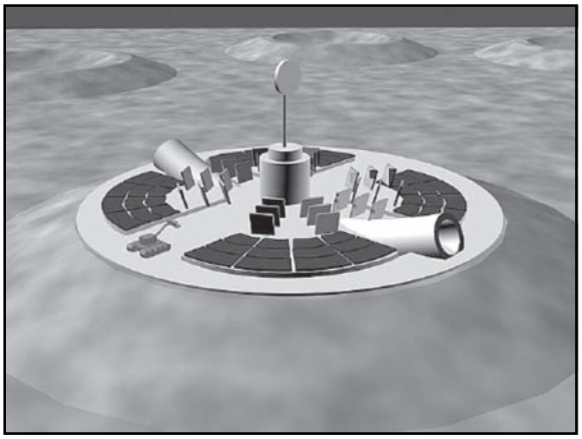


Figure 3.78. Depiction of the functioning lunar self-replicating factory. (courtesy of Chirikjian group,[980] © 2002 IEEE)

4. **Electromagnetic Rail Guns**. A novel aspect of this design proposal is the use of integral railguns for long-distance transportation of daughter factories to distant points on the moon, or for sending materials to low Earth orbit (LEO). In this concept, when a replica is ready to be transported to a new location, all of its subsystems are packed into an iron casing, accelerated like a bullet train and shot ballistically like a cannon ball, eventually falling to ground at its new location. Since a railgun can consist of many identical units, and since the gun is not required to manufacture the replica, there is no need to send a whole railgun to the moon. Only one section of the railgun need be sent, and from this section a mold can be made which can then be replicated to construct the full railgun. A mathematical model of the proliferation of self-replicating robotic factories across the lunar surface suggests that railgun pointing errors can influence the evolution of factory locations but that over time, the probability distribution converges to a uniform distribution more quickly for railguns with noisier pointing accuracies.

3.25 NIAC Phase I Studies on Self-Replicating Systems (2002-2004)

The NASA Institute for Advanced Concepts (NIAC) is a research institute within the Universities Space Research Association (USRA).[1294] USRA is a private nonprofit corporation, charged with the "development of knowledge associated with space science and technology" under the auspices of the National Academy of Sciences, that includes 84 universities and research institutes in the United States, two member institutions in Canada, two in England, and two in Israel. NIAC's charter is to focus on grand, revolutionary, longer-term concepts for architectures and systems potentially useful in space science and technology.

In recent years, four NIAC grants, summarized below, have been awarded to researchers who are studying kinematic self-replicating machines. As these words are written, the latter three of the four studies are still in progress.

3.25.1 Lipson Self-Extending Machines (2002)

Following in the tradition of the 1980 NASA replicator study which adopted 100% materials closure as its goal (Section 3.13), Hod Lipson at Cornell University was awarded a Phase I NIAC contract to study "Autonomous Self-Extending Machines for Accelerating Space Exploration" during 1 May 2002 through 31 October 2002.[1295,1296] This work expanded an earlier discussion by Lipson and Pollack[927] of the "self-extending machines" concept, wherein robots evolve from basic building blocks using rapid manufacturing technologies.

According to the study abstract: "The rate at which we explore planets is tightly linked with the rate at which we are able to successfully complete robot deployment cycles. Judging from past experiences of Mars and Lunar explorations, the design-fabricate-test-deploy cycle takes an order of a few years to complete at least. The approach advocated here shifts the focus from designing and launching the ultimately capable and robust robot, to launching a fabrication system that can fabricate and recycle task-specific robots in the field, as well as extend its own capabilities. In this vision, a self-contained fabrication facility is launched with initial material and component stock. Tested blueprints are transmitted subsequently for fabrication on site, as appropriate to exploration state and findings. Materials and components recycled from the original spacecraft, unused robots and in-situ resources of energy and material are used to construct newer machines as required. The focus of this proposal is on the architecture of a 100% automatic, self-contained and versatile fabrication process, capable of autonomously producing an entire working machine with no human intervention. This proposal is well grounded in the physics of new multi-functional materials and free-form fabrication, yet the focus on fully autonomous fabrication of complete systems is a uniquely new and enabling challenge that has not been addressed before. This phase will deliver two parts: (a) an architecture of a fully autonomous deployable self-extending machine, along with a comprehensive study of required functionalities and candidate materials and components, and (b) an evaluation of the architecture through a limited concept implementation. The goal is to allow an informed assessment of the merits of this approach, and decision as to pursuing a second phase of investigation validating fully autonomous fabrication of complete working robots involving actuation, sensing and logic. This research will help NASA achieve its goal of completing missions more frequently, less expensively, and with greater flexibility."

3.25.2 Chirikjian Self-Replicating Lunar Factories (2003-2004)

As a continuation of the work described in Section 3.24, Gregory Chirikjian at Johns Hopkins University was awarded a Phase I NIAC contract to study "Architecture for Unmanned Self-Replicating Lunar Factories" during 1 October 2003 through 31 March 2004.[1297]

According to the study abstract: "The goal of this proposal is to analyze the feasibility of a fully automated robotic factory system for the development of lunar resources, and the transportation of those resources to low-Earth orbit. The key issue that will determine the feasibility of this approach is whether or not an autonomous robotic factory can be devised such that it is small enough to be transported to the moon, yet complete in its ability to self-replicate with no other inputs than what is available on the lunar surface. Self-replication leads to exponential growth, and would allow as few as one initial factory to spawn lunar production of materials and energy on a massive scale. Such capacity would dramatically impact man's ability to explore and colonize space, as well as to deliver hydrogen and oxygen to fuel the fledgling industries that will develop in low-Earth orbit over the next few decades.

"Our architecture for a self-replicating robotic factory system consisted of five subsystems: (1) multi-functional robots for digging and transportation of materials, and assembly of components during the replication process; (2) materials refining plant; (3) parts manufacturing facility; (4) solar energy conversion, storage and transmission; (5) electromagnetic guns for long-distance transportation (e.g., for sending materials to low-Earth orbit, or transporting replicated factories to distal points on the moon). We envision that a fully functional lunar factory site will occupy approximately one square kilometer. However, the precursor that is launched from the earth will be a minimalist system consisting only of two robots, a small furnace, molds, mirrors and solar panels and weighing between five and ten metric tons. The full self-replicating robotic factory will be constructed under remote control from the earth using the precursor system."

After the Phase I study was completed in March 2004, the Final Report[1297] concluded: "The key issue to determine the feasibility of this approach in the NIAC time frame was whether or not complementary technologies expected over the next 10 to 40 years would exist for an autonomous robotic factory to function. In particular, it was not clear a priori whether such a system could be devised such that it would be small enough to be transported to the moon, yet complete in its ability to self-replicate with little input other than what is available on the lunar surface. Minimalist systems which can be launched at low cost, harvest lunar resources, and bootstrap up to a substantial production capability are appealing. Self-replication leads to exponential growth, and would allow as few as one initial factory to spawn lunar production of materials and energy on a massive scale. Such capacity would dramatically impact man's ability to explore and colonize space, as well as to deliver hydrogen and oxygen to fuel interplanetary spacecraft and the fledgling industries that will develop in space over the next few decades. This report has shown using a combination of prototype implementations, analysis, and literature survey that self-replicating lunar factories do in fact appear to be feasible. A road map for the novel recombination and integration of existing technologies and systems into an architecture that can be implemented in the next ten to forty years is provided.

"Many technological hurtles must be overcome before self-replicating robots can become a reality, and current knowledge from many diverse disciplines must be recombined in new ways. In this Phase I feasibility study we examined what lunar resources can be exploited, and investigated "toy" designs for robots with the ability to self-replicate. To this end, we examined how each subsystem of a robotic factory (motors, electronic components, structural elements, etc.) can be constructed from lunar materials, and demonstrated these ideas in hardware. We did this at several levels. For example, robots that assemble exact functional copies of themselves from pre-assembled subsystems were demonstrated. The feasibility of assembling an actuator from castable shapes of structural material and molten metal was demonstrated with proxy materials. The assembly of simple self-replicating computers made of individual logic gates was demonstrated. A strategy was developed for how the lunar regolith can be separated into ferrous, nonferrous conducting, and insulating materials in the absence of water was studied and partially demonstrated. In addition, the energy resources available at the lunar surface were evaluated, means for using this energy were developed, and the energetic requirements of various subsystems were computed. Our conclusion is that the proposed system architecture indeed appears to be feasible provided certain existing technologies can be integrated in new ways."

The control systems for the mobile lunar robots are to be constructed using electromechanical relays and vacuum tubes, providing simple (though bulky) electronic logic circuits that are readily fabricated using lunar materials. As a preliminary demonstration, Chirikjian's group has built several exemplar "self-replicating circuits" using transistors embedded in LEGO® blocks.[2339-2341] In one case,[2340] the physical implementation consisted of a robotic system and a conveyor belt system for replicating its code and circuit, plus the initial code and the circuit to be replicated. During replication, "a conveyor belt feeds the code one line at a time to the reader array. The array then sends the code signal to the control circuit. The signal is decoded as any of seven robot arm or position movements. The robot then carries out the movement command. The commands would tell it to go to one of three feeder positions, pick up the items at that position, move to the assembly line, and drop the items into place. The next set of codes is then fed to the readers, and the process would repeat."

3.25.3 Todd Robotic Lunar Ecopoiesis (2003-2004)

Paul Todd at Space Hardware Optimization Technology (SHOT), Inc. was awarded a Phase I NIAC contract to study "Robotic Lunar Ecopoiesis" during 1 October 2003 through 31 March 2004.[1298] The proposal illustrates a biological approach to kinematic replication.

According to the study abstract: "The long-term concept is to let a living ecosystem create itself in an engineered dome on the Moon under controlled Mars-like conditions. Under robotic control, a community of organisms creates its own environment that is no longer hostile to living things. For example, the energy to self-construct the bubble is initially obtained from fuel cells that also produce the water that the enclosed system will use to moisten the regolith. Initially, robotically controlled bottled gases will control the internal pressure at 1.0-1.5 kPa, heat from the Sun will be controlled by radiators initially actively positioned by photovoltaic electric motors or solar-powered Stirling engines. Then chemoautotrophic microorganisms gain energy from the lunar regolith producing organic matter for fungi, which produce CO_2 for algae, which will produce O_2 for some simple invertebrate animals. This would be a precursor to terraforming studies (fairly controversial) for Mars, but accessible and controllable owing to the relative proximity of the Moon. This approach differs from the Closed Environment Life Support Systems (CELSS) approach in that the Ecopoiesis Test Bed is an architecture that causes the environment to evolve on its own, starting with water and nitrogen and spores or inactive cells of appropriate prokaryotes, seeds, and eggs of organisms that eventually occupy the module. Experimental ecopoiesis is a new field, so experiments will begin in the laboratory and evolve to ISS (International Space Station) in at least three phases before a lunar module is considered. A gradual, stepwise multi-year approach is proposed, in which Phase I is a feasibility study, Phase II consists of laboratory experiments and spaceflight planning, and Phase III is a multi-institution undertaking of indefinite duration culminating with a robotic lunar ecopoiesis laboratory.

3.25.4 Toth-Fejel Kinematic Cellular Automata (2003-2004)

Building on his KCA concepts described in Section 3.8, Tihamer Toth-Fejel at General Dynamics Advanced Information Systems was awarded a Phase I NIAC contract to study "Modeling Kinematic Cellular Automata: An Approach to Self-Replication" during 1 October 2003 through 31 March 2004.[1299]

According to the abstract of the original proposal, the study will "design a useful Self-Replicating System (SRS). As shown by NASA's summer study Advanced Automation for Space Missions[2] and other smaller studies, the development of dynamically reconfigurable SRSs that implement Universal Constructors can revolutionize future space missions. For example, a self-replicating lunar factory could build solar cells and other manufactured tools with which to explore and develop the Moon with exponential growth. But despite the fact that these studies showed the tremendous power of machine self-replication, there have been no serious attempts to further the field. However, two recent small efforts (Sections 3.18 and 3.23) have resulted in some success. We propose to build upon one of those successes by designing a system of Kinematic Cellular Automata (KCA) cells that are configured as a limited implementation of a Universal Constructor. The trivial self-replication is easy, but the final goal of autotrophic self-replication is certain to be extremely difficult. So there is a huge unexplored area between these two extremes, and we believe that an iterative approach of gradually moving complexity out of the environment and into the cell is the best chance at characterizing it."

"[The work will] start by simulating a trivial self-replication process in a 3-D world that is as simple as possible — a KCA in a moving gantry/arm configuration placed in an environment full of inert cells (the zero-complexity scenario). After this testbed simulation confirms the KCA reconfiguration algorithms, the one-complexity scenario will start with each inert cell divided in half, and the gantry/arm KCA will assemble these subcomponents into complete KCAs before reconfiguring them into another KCA. After successfully developing the algorithms necessary, the dividing iteration will be repeated for the two-complexity scenario. The idea is to move the complexity out of the environment and into the cell, ultimately towards a system that requires only feedstock molecules, energy, and information to build copies of itself and any of a wide variety of other products. As a bonus, developing each successful scenario will result in both hardware designs of useful modular robots and the control algorithms that run them."

According to the Final Report,[1299] Toth-Fejel's analysis showed that the complexity of a useful KCA replicator can be less than that of a Pentium IV microprocessor. For instance, the helical stacking of passive domino-shaped alternating bricks of metal and insulator material yields an astonishingly simple and robust design for an electromechanical solenoid actuator that would seem to require very little manufacturing sophistication to fabricate. The study also developed a reasonable hierarchy for a practical replicator system including a workable preliminary design that could be applied at macro, micro, and nano scales. In this view, a KCA replicating system is a hierarchy consisting of subsystems which are made up of Cells (Figure 3.79), which are made up of Facets, which are made up of Parts, which are made up of self-assembled Subparts — and at the bottom, everything is made of molecules. During replication the system assembles simple inert *parts* into symmetrical *facets* that form modular dynamic *cells* that are configured as Connector, Transporter, and Controller *subsystems* to make up a Self-Replicating System (SRS).

Toth-Fejel's **Transporter subsystem** design consists of less than 12 cells, two of which grab parts, one at a time, and three on the bottom which actually move the subsystem around on a "base plane" of about 50 cells. The **Connector subsystem** serves to connect Parts — while each Transporter is composed of 12 cells that moves one part around, a Connector contains a Transporter for each part that it connects, plus one Transporter for each preparation tool. For the **Controller subsystem**, Configurable Logic Blocks (of which 120 are needed to implement the tiny 8-bit PicoBlaze processor) are employed that are functionally identical to those in existing implementations of Field Programmable Gate Arrays (FPGAs), thus allowing the use of commercially available VHDL (VLSI Hardware Description Language) interpreters that can automatically specify the necessary connections between the CLBs, and also allowing the use of other existing soft processor peripherals which means that the software for a large class of Utility Fog (Section 3.8) configurations already exists. The study focused much attention on achieving closure at a digital information level. For instance, a design for a simple op-amp consists of a mosaic of 50 Wang tiles of 11 different tile types, each tile a very simple and easily-manufactured cell having the functionality of, for example, a wire and transistor; a similarly designed NAND gate is an array of 42 Wang tiles of 8 different tile types (Figure 3.80). Dozens of specific control-sequence subroutines, listed in an Appendix A of the Final Report,[1299] were written to simulate (and visualize) one complete assembly operation using a Transporter and Connector

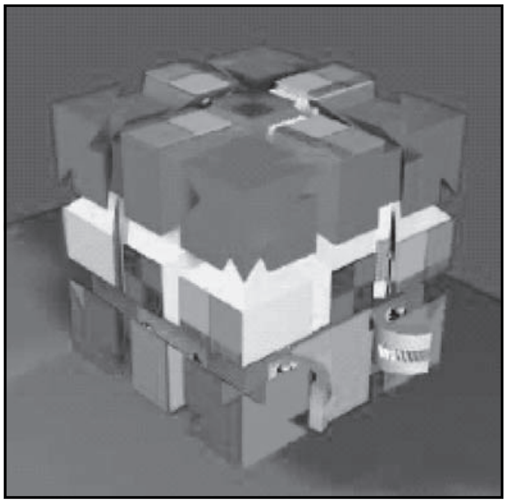
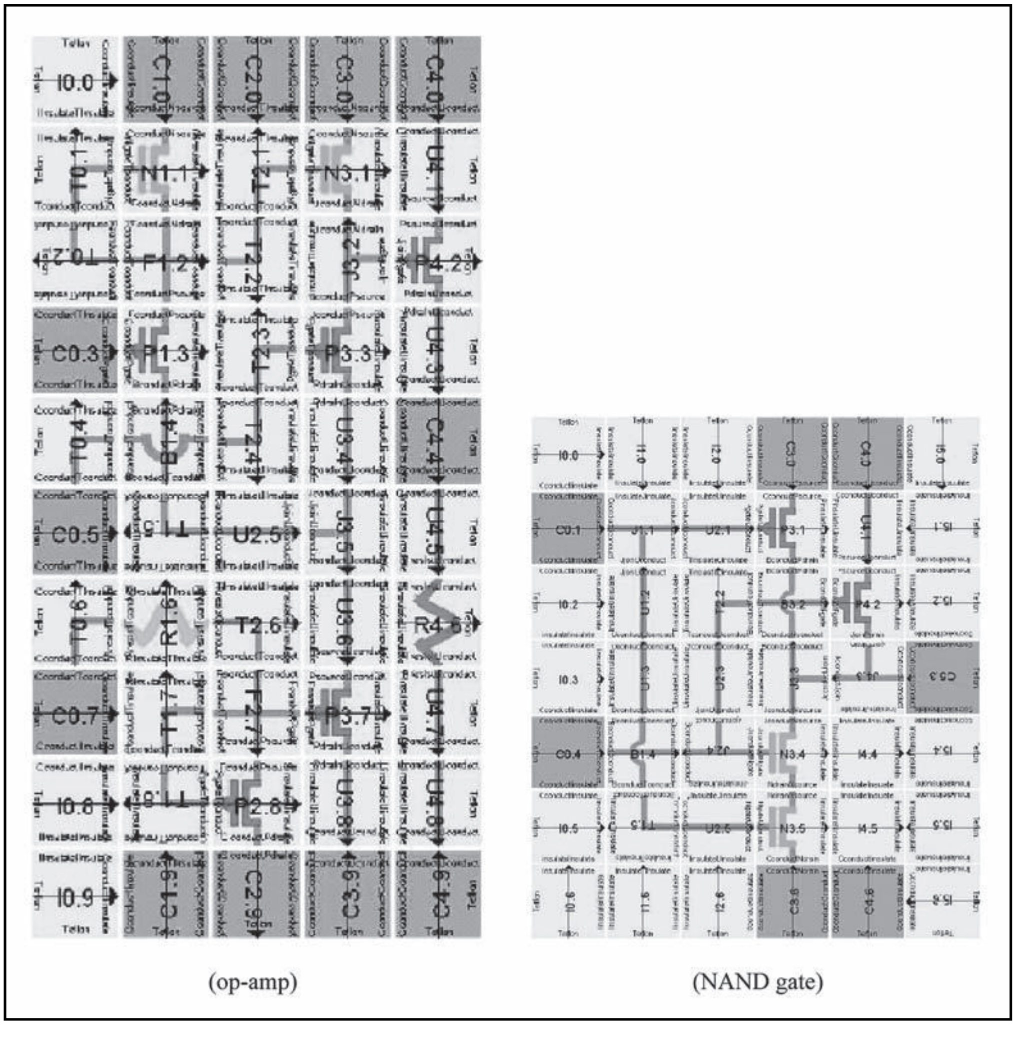


Figure 3.79. KCA unit cell with some tabs and sensors. (image courtesy of Tihamer Toth-Fejel[1299])



(op-amp) (NAND gate)

Figure 3.80. Wang-tile implementations of an op-amp (left) and a NAND gate (right), using KCA cells configured as electronic wire/transistor components. (images courtesy of Tihamer Toth-Fejel[1299])

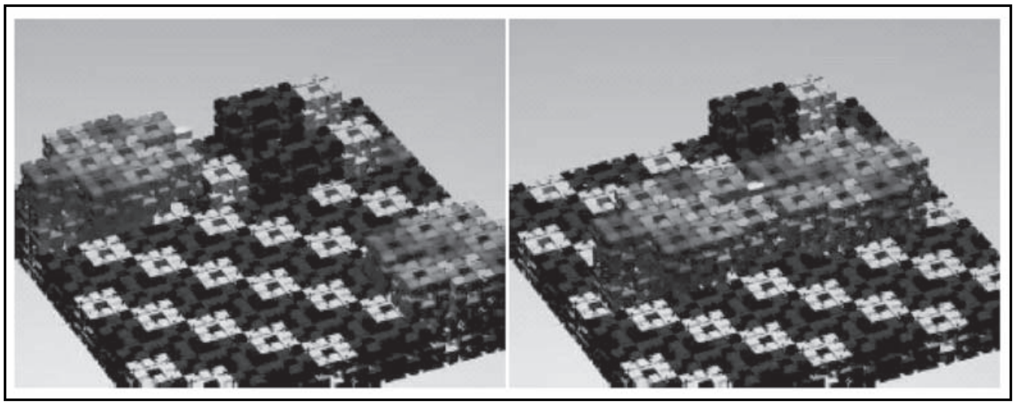


Figure 3.81. Two steps among many, in a lengthy parts assembly operation involving KCA cells on a base plane platform. (images courtesy of Tihamer Toth-Fejel[1299])

(Figure 3.81). Noted Toth-Fejel:[1299] Only a small number of [these subroutines] needed to be implemented in MaxScript to simulate an assembly process. Surprisingly few subroutines were necessary to code this simulation. Hundreds of steps very similar to this assembly step would be necessary to build a single modular cell.

One of the authors of this book (Freitas) served as a technical consultant for this study, along with Matt Moses as the second consultant.

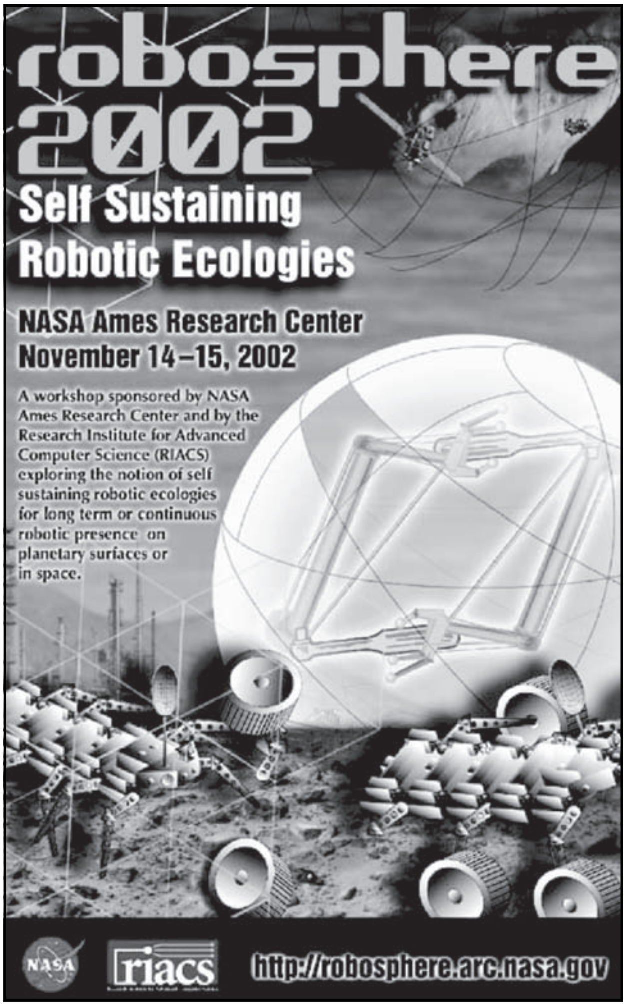
3.26 Robosphere Self-Sustaining Robotic Ecologies (2002-2004)

In November 2002, Silvano P. Colombano, a computer scientist at NASA/Ames Research Center, organized the first workshop on self-sustaining robotic ecologies called "Robosphere 2002" (Figure 3.82),[1300] with a second workshop scheduled for November 2004[1301] and longer-term plans for a facility (Robosphere1) for experimentation on self-sustaining robotic activities and a virtual Robosphere environment (VRobosphere) for simulations at NASA. The stated purpose of the Robosphere effort is to "explore the possibility of long term or continuous robotic presence on planetary surfaces and in space, in order to increase scientific returns, decrease exploration costs and greatly decrease any chances of mission failures. The underlying notion is that of self-sustaining robotic ecologies, where the continuous survival and exploration activities of robotic teams and colonies are dependent on the exchange of matter, energy and information among robotic individuals and 'species'."

Topics discussed at the 2002 Robosphere workshop included:

1. Small robotic teams capable of mutual repair (modular robotics; reconfigurable robotics; self-repair, recycling and self-replication);
2. Robotics outposts (functional specialization; energy production; shelter construction (for robots); utilization/production of parts);
3. Planetary robotic infrastructures (robotic "oases"; robotic "highways"; robotic "factories"; scientific exploration infrastructure; communications/networks); and
4. Robotic colony autonomy (distributed planning and scheduling; mixed-initiative planning; distributed execution monitoring and diagnosis; self-organization and cooperative strategies; colony models from biology and ecology, swarms; robotic ecologies with different scales, from rovers to nanorobots).

Papers were presented on self-replicating robots,[977] robotic fabrication[1302] and robotic assembly,[1303] robotic ecologies,[1304,1305] self-reconfiguring robots,[1306] and autonomous robotics.[1307,1308]



robosphere 2002

Self Sustaining Robotic Ecologies

NASA Ames Research Center
November 14–15, 2002

A workshop sponsored by NASA Ames Research Center and by the Research Institute for Advanced Computer Science (RIACS) exploring the notion of self sustaining robotic ecologies for long term or continuous robotic presence on planetary surfaces or in space.

http://robosphere.arc.nasa.gov

Figure 3.82. Robosphere 2002 workshop on self-sustaining robotic ecologies, courtesy of Silvano Colombano.[1300]

3.27 Lozneanu-Sanduloviciu Plasma Cell Replicators (2003)

According to a report from *New Scientist*,[1309] Lozneanu and Sanduloviciu[1310] at Cuza University in Romania have created spheres of gaseous plasma that can grow, replicate and communicate, thus "fulfilling most of the traditional requirements for biological cells" although without inherited material they cannot be described as alive. The physicists studied environmental conditions similar to those that might have existed on the primordial Earth when the planet was enveloped in electric storms that allowed ionized plasmas to form in the atmosphere. Two electrodes were inserted into a chamber containing a low-temperature argon plasma of argon. After a high voltage was applied to the electrodes, the resultant electrical arc passing through the gap between the electrodes caused a high concentration of ions and electrons to accumulate at the positively charged electrode which spontaneously formed spheres having a boundary made up of two layers — an outer layer of negatively charged electrons and an inner layer of positively charged ions, with an inner nucleus of gas atoms trapped inside the boundary. The researchers grew spheres from a few microns up to three centimeters in diameter, with the cell-like self-organization occurring in a few microseconds and the amount of energy in the initial spark governing cell size and lifespan.

A distinct boundary layer that confines and separates an object from its environment is one of the main criteria customarily used to define living cells, so Lozneanu and Sanduloviciu examined whether their plasma cells could meet the other criteria for "life", i.e., the ability to replicate, to communicate information, and to metabolize and grow. They found that the spheres could replicate via binary fission, and also could grow larger under the right conditions, taking up neutral argon atoms and splitting them into ions and electrons to replenish their boundary layers. Finally, the plasma cells could communicate information by emitting electromagnetic energy, making the atoms within other spheres vibrate at a particular frequency. The plasma spheres are evidently the first "gaseous cell" self-organizing systems to meet all of these requirements.

The possibility of self-replicating plasma balls and gas clouds has a long history in science fiction,[1311] and the idea of self-replicating stars[268] in conventional astrophysics has already been mentioned in Chapter 1.

3.28 Griffith Mechanical Self-Replicating Strings (2003-2004)

Saul Griffith[1312] (see also Section 4.1.5) is interested in the minimal logic required to exhibit physical self-replicating behavior, in the tradition of the Penrose block systems (Section 3.3). Griffith asserts that if the logical overhead is low enough, then self-replication has potential in a manufacturing sense. Griffith further constrains the problem to be addressed by requiring, first, that the self-replication should be arbitrary (i.e., the system can replicate a physical object of arbitrary complexity) and, second, that the replicated object should be able to conform to an arbitrary 2-dimensional or 3-dimensional geometry. Penrose completed his work at a time when state machines and the language to describe them were just being developed so it is not surprising that his description of his mechanisms offers no easily discernible blueprint for a more general logical design. The following material in this Section, describing a physical realization of a simple but general-purpose KCA self-replicating system, is largely excerpted from research notes generously shared with one of the authors (Freitas) by Griffith.[1312]

A key aspect of Griffith's designs is the memory requirement for replication. If each part of an assembly must retain the entire code for the assembly, then each part must have a memory capacity capable of storing that description. In biology, every cell does contain the entire code for the assembly, albeit at a coarser scale of assembly in the multi-tiered assembly design of biological entities, but at the subcellular level a different memory management scheme is used in which the "memory" is contained within the structure itself (i.e., the code within the base pairs of DNA). This localized copying/complementarity method can also be used in either 1-D (linear) or in 2-D (planar) nonbiological systems. A 1-D system will look very similar to DNA except that complementarity is not necessary and we can template an exact copy, not a compliment; a 4-base system is not strictly necessary because a 2-base (binary) system is sufficient. A 2-D, or planar, system would look like a programmed or templated "plating" type system. The difficulty in plating-type replication is in the termination signal, where the copy is to separate from the original to make way for a subsequent round of replication. Griffith[1312] observes that a 3-D system is not amenable to this replication treatment because not all of the structure is available at the surface of the assembly and therefore some of the information within the structure would need to be transferred (and stored in memory) through outer layers of the assembly. He notes: "It may be stating the obvious, but this is probably why biological replicating systems use linear assemblies for replication that can subsequently fold into 3-D structures (or unfold for replication)."

There are two ready approaches to basic replication, among others. In the first approach, the individual units of the assembly are state machines capable of selecting and copying similar units in a similar assembly. The biological analogy to this can be thought of as an RNAase-less RNA replication where the RNAase's logical function of selecting and adding base pairs is performed by state machines within each base. In the second approach (more similar to biological systems), the logical machinery is the RNAase which assembles more basic units into a second RNAase, and so forth. These two approaches might be described as distributed logic replication and centralized logic replication. In the former, the logic requirements are performed by cellular automaton-type nearest-neighbor interactions between the cells. In the latter, the copying assembly (or RNAase equivalent) is the central processor that reads and copies the data tape. Griffith has concentrated his efforts on the distributed logic replication approach, in an attempt to design the minimal logical units for a replicating system capable of replication of an arbitrarily complex structure containing an arbitrarily complex string of assembly instructions. To represent the data string, Griffith uses two types of components which can be similar logically but must differ in some important way (e.g., shape selectivity) to enable subsequent processing.

In his logic design for a parallel-replication 4-edge/3-neighbor system, Griffith uses a cellular automaton representation of the logical requirement for a linear templating replication. The diagram in Figure 3.83 shows the physical process of the replication. Each individual sub-unit or "cell" is represented as a box. A "1" represents an edge in an attractive state, attracting and binding random untethered cells. A "0" represents a neutral edge state where no binding will occur. A line between two cells represents a tethered bond — tethered bonds occur at the junction between any two edges in the "1" attractive state, such as "1 — 1". A free floating unit cell is always in the (0, 0, 0, 0) state. A "1" edge will attract a "0" edge but not bind it. A "1" edge will bind to another "1" edge. "0" edges neither attract nor bond. The first steps in the replication are numbered from 1 to 10. Note that this system is replicating an original input string of 5 cells (in the upper row), but in fact scales to strings of arbitrary length.

This mathematical representation employs the concept of cellular automata (Sections 2.1.3, 2.2, and 3.8). The self-replicating wire (Figure 3.84, topmost) is first filled with the initial values of the cells. The wire has 4 rows: the first two rows represent the cells of the original programmed string and the last two rows represent the replicating string. The orientation of the states of the cells is different for the programmed string and for the replication string. This is mainly because communication-intensive edges of neighboring cells must be arranged close to each other in order to keep the bits of each rule to a minimum. (This is convenient when mechanically implementing this design, wherein the geometry of the cell tiling is

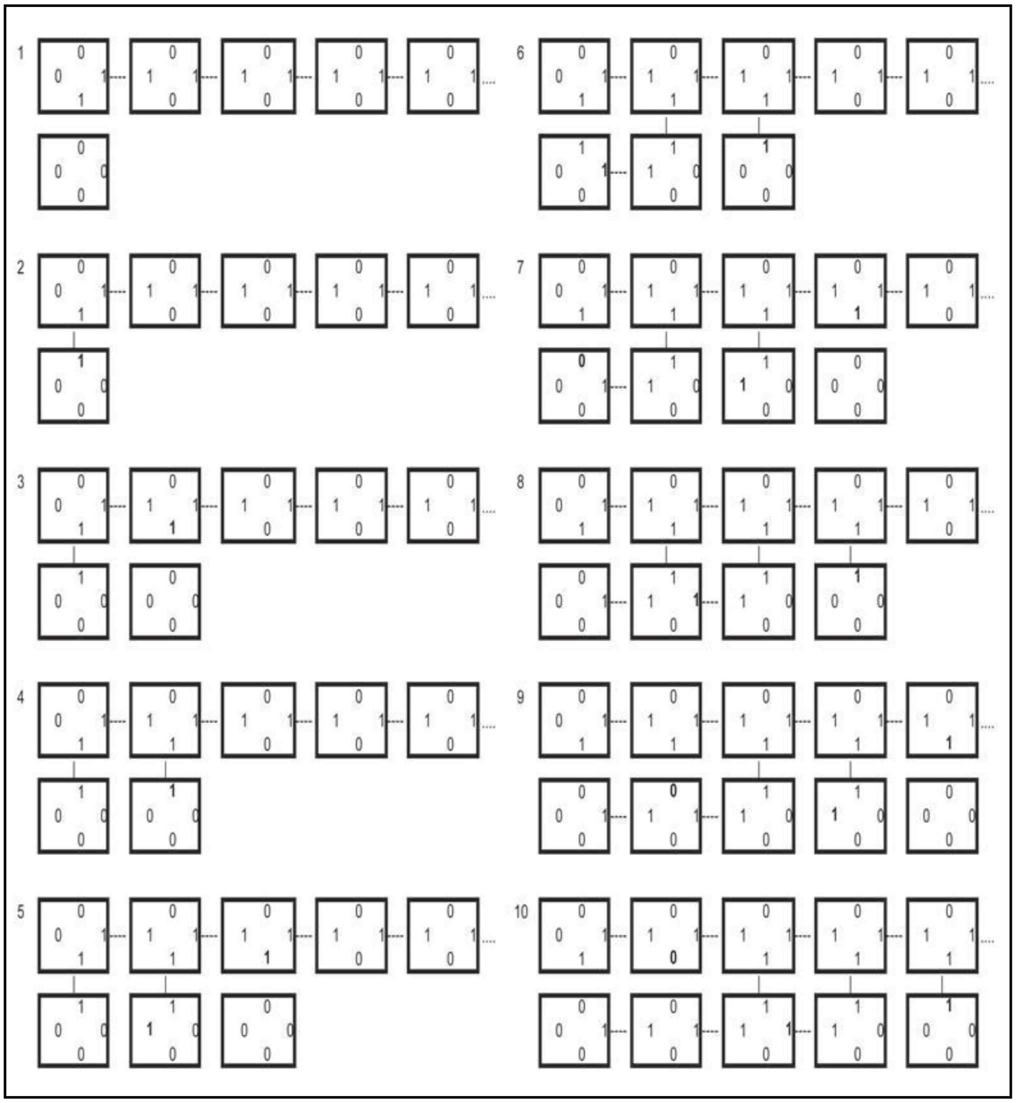


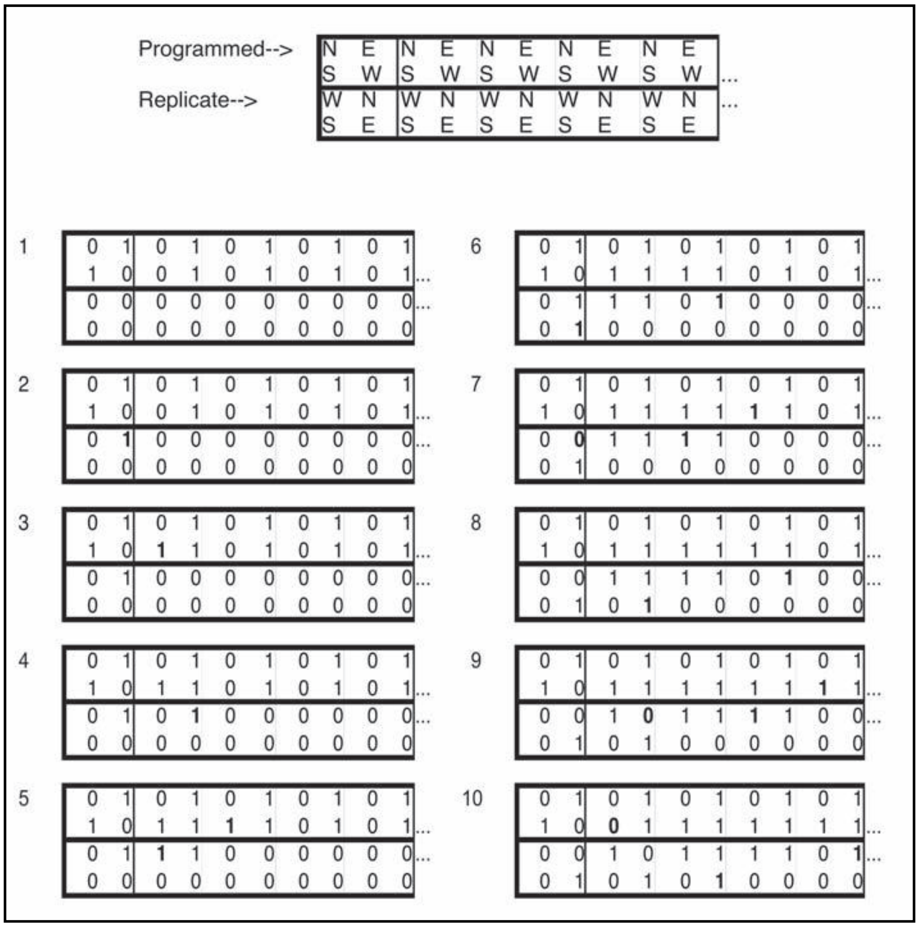
Figure 3.83. Cellular automaton representation of Griffith linear templating replication. (image courtesy of Saul Griffith[1312])

important in minimizing the number of states.) The topmost diagram in Figure 3.84 shows the actual orientation of the states of each cell — N stands for the state of the north edge, S for the state of the south edge, and so on. Notice that the division at the end of the replicating steps can be shown easily by simply dividing the wire horizontally in the middle: the top two rows will be the original programmed string and the bottom two will be the copied string. The quiescent space outside the wire is filled with 1's. The updating of the wire itself is shown below. Each update is of one cycle, starting from the initial state.

The effective rule table for Griffith's replicating-string automaton is shown in Figure 3.85. Here, the "cycle" number refers back to each numbered image in Figure 3.84. There can be multiple logical steps at each cycle. In this rule table, the central value (second row, third column) is the one that's changing in relation to its 9 neighbors (8 nearest neighbors and 1,2-distance neighbor to the left). This central value changes to the value indicated to the right of the arrow. While we typically conceive of a cellular automaton as a clocked updating of all cells at a regular interval, the scheme presented here is a self-clocking or "asynchronous" cellular automaton. Physically, this means that in a replicating system such as the original input string, which is floating in a bath of loose unbound cells, the clocking and logical operations occur upon the binding of a cell to the replicating string. It is important to note that the copying proceeds from left to right, and that at any given moment in the replication the replicating string is tethered to the input string by just a single bond at the site of the most recent cell addition. Note also that in cycle 8 the rules start to repeat. This is because the replication process can be arbitrarily long, but the general algorithm for updating the wire remains the same.

Since it is somewhat difficult to interpret the physical meaning of these rules simply by looking at the rule table, Griffith has built a physical mechanism that can execute this logic. One of the first choices in the design of this mechanism was the tiling scheme. The main constraint is that any logical operation should not be passed through another tile as that would require vias, memory, or logic within that cell. The logic designed above requires communication with 4 neighbors, so a tiling design enabling 4 contact-face neighbors and single-axis 4-neighbor contacts was desirable. Accordingly, the T-shaped tiles shown in Figure 3.86 achieve both goals — there are 4 contact-face neighbors, and all of those contacts can be executed on faces lying in one axis. The bottommost diagram in Figure 3.86 shows the logical routing. Arrowheads represent the opening of a gate for binding, while the origin of the line with the arrowhead represents the input connection that forces this change of state. The input of a connection can be thought of as routing a switch from a "0" to a "1" state (open for binding) at the arrowhead.

The first mechanical implementation of this design used LEGO® blocks with laser-cut custom parts in acrylic (Figure 3.87). The



Programmed-->	N	E	N	E	N	E	N	E	N	E	
	S	W	S	W	S	W	S	W	S	W	...
Replicate-->	W	N	W	N	W	N	W	N	W	N	...
	S	E	S	E	S	E	S	E	S	E	

1	0	1	0	1	0	1	0	1	0	1	
	1	0	0	1	0	1	0	1	0	1	...
	0	0	0	0	0	0	0	0	0	0	...
	0	0	0	0	0	0	0	0	0	0	

2	0	1	0	1	0	1	0	1	0	1	
	1	0	0	1	0	1	0	1	0	1	...
	0	**1**	0	0	0	0	0	0	0	0	...
	0	0	0	0	0	0	0	0	0	0	

3	0	1	0	1	0	1	0	1	0	1	
	1	0	**1**	1	0	1	0	1	0	1	...
	0	1	0	0	0	0	0	0	0	0	...
	0	0	0	0	0	0	0	0	0	0	

4	0	1	0	1	0	1	0	1	0	1	
	1	0	1	1	0	1	0	1	0	1	...
	0	1	0	**1**	0	0	0	0	0	0	...
	0	0	0	0	0	0	0	0	0	0	

5	0	1	0	1	0	1	0	1	0	1	
	1	0	1	1	**1**	1	0	1	0	1	...
	0	1	**1**	1	0	0	0	0	0	0	...
	0	0	0	0	0	0	0	0	0	0	

6	0	1	0	1	0	1	0	1	0	1	
	1	0	1	1	1	1	0	1	0	1	...
	0	1	1	1	0	**1**	0	0	0	0	...
	0	**1**	0	0	0	0	0	0	0	0	

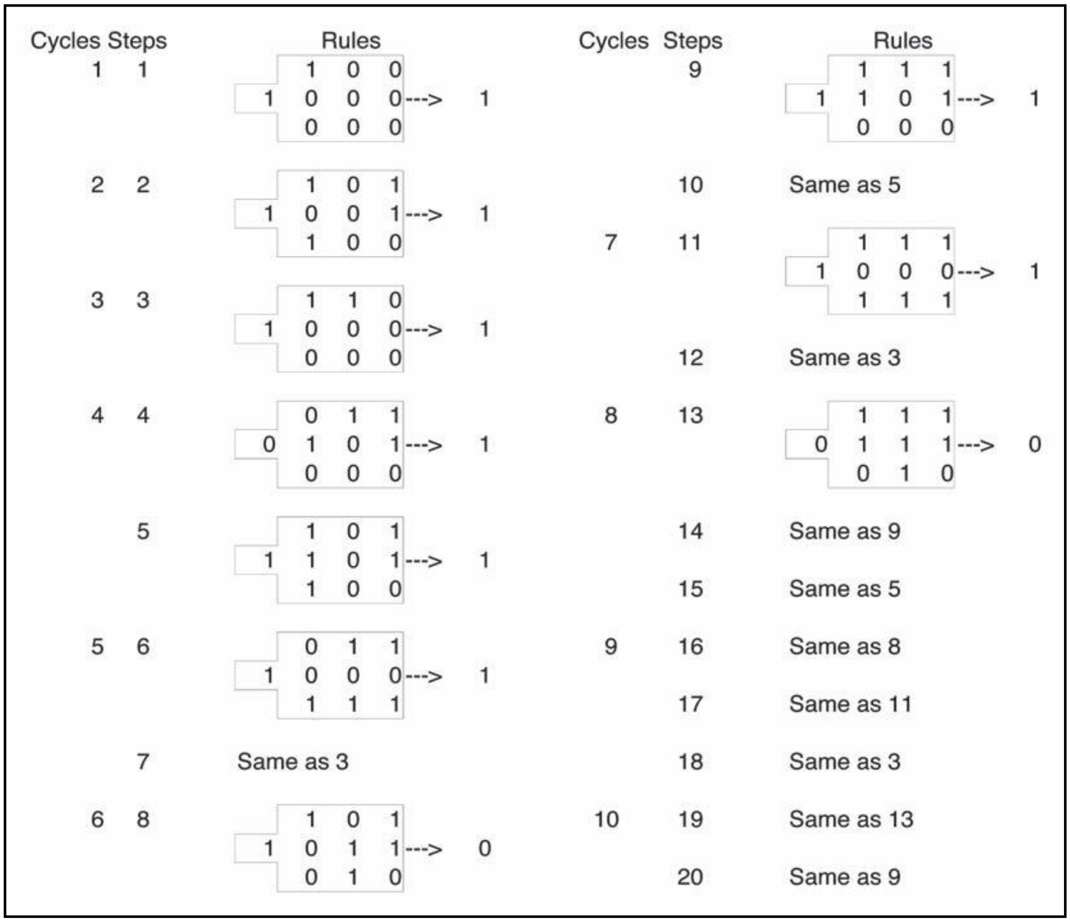
7	0	1	0	1	0	1	0	1	0	1	
	1	0	1	1	1	1	**1**	1	0	1	...
	0	**0**	1	1	**1**	1	0	0	0	0	...
	0	1	0	0	0	0	0	0	0	0	

8	0	1	0	1	0	1	0	1	0	1	
	1	0	1	1	1	1	1	1	0	1	...
	0	0	1	1	1	1	0	**1**	0	0	...
	0	1	0	**1**	0	0	0	0	0	0	

9	0	1	0	1	0	1	0	1	0	1	
	1	0	1	1	1	1	1	1	**1**	1	...
	0	0	1	**0**	1	1	**1**	1	0	0	...
	0	1	0	1	0	0	0	0	0	0	

10	0	1	0	1	0	1	0	1	0	1	
	1	0	**0**	1	1	1	1	1	1	1	...
	0	0	1	0	1	1	1	1	0	**1**	...
	0	1	0	1	0	**1**	0	0	0	0	

Figure 3.84. Logical scheme and replication cycle of Griffith self-replicating wire. (image courtesy of Saul Griffith[1312])



Cycles	Steps	Rules		
1	1	1 0 0 1 0 0 0 0 0 0	--->	1
2	2	1 0 1 1 0 0 1 1 0 0	--->	1
3	3	1 1 0 1 0 0 0 0 0 0	--->	1
4	4	0 1 1 0 1 0 1 0 0 0	--->	1
	5	1 0 1 1 1 0 1 1 0 0	--->	1
5	6	0 1 1 1 0 0 0 1 1 1	--->	1
	7	Same as 3		
6	8	1 0 1 1 0 1 1 0 1 0	--->	0

Cycles	Steps	Rules		
	9	1 1 1 1 1 0 1 0 0 0	--->	1
	10	Same as 5		
7	11	1 1 1 1 0 0 0 1 1 1	--->	1
	12	Same as 3		
8	13	1 1 1 0 1 1 1 0 1 0	--->	0
	14	Same as 9		
	15	Same as 5		
9	16	Same as 8		
	17	Same as 11		
	18	Same as 3		
10	19	Same as 13		
	20	Same as 9		

Figure 3.85. Effective rule table for Griffith self-replicating wire. (image courtesy of Saul Griffith[1312])

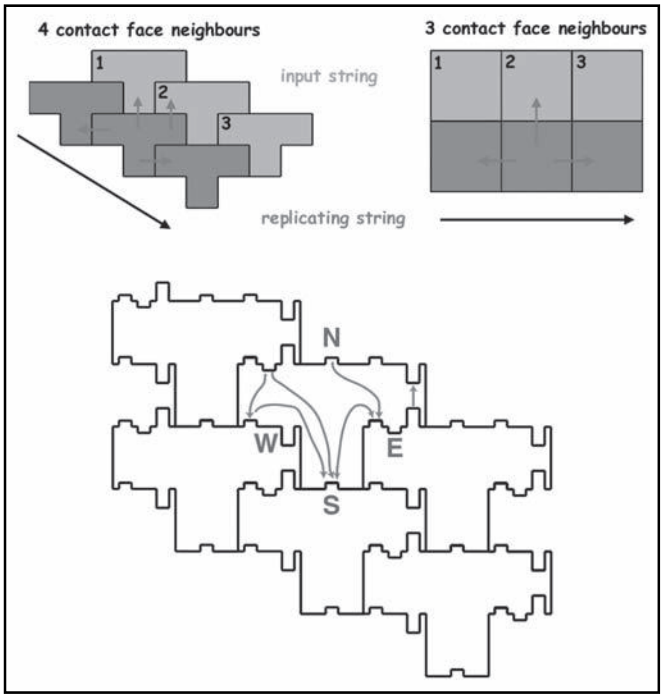


Figure 3.86. Tiling scheme for Griffith self-replicating wire. (image courtesy of Saul Griffith[1312])

physical scale is roughly 3 x 4 inches for the whole cell (leftmost image). The three rightmost images demonstrate the replication sequence for a dimer. The blue and pink units display exactly the same logic as represented earlier. The only difference is a mechanical shape selectivity that prevents pink binding to blue, and vice versa. One can now see how a bit string of data can be replicated by such a system. Any arbitrary input string of pink and blue tiles can be replicated in the lower string. Note that at the completion of the final cell in the replicating string, the two strings automatically divide into two complete strings ready for the next round of replication. Note also that this system is very simple, representing only 5 discrete states. In late 2003, Griffith reported[1312] that further work then in progress would lead to more complex replicating string designs, the details of which would probably be published in 2004 as part of his Ph.D. dissertation.

The significance of this work is clear, says Griffith:[1312] "With such low costs for digital logic, why concern ourselves with minimal state machines for replication? Concerted engineering efforts over the last 50 years have reduced the cost of silicon-based digital logic to extremely low levels. Basic microcontrollers with a lot of memory (by replication standards) and fully Turing-complete are available for under $1 each; if packaging costs didn't dominate as the size is shrunk, they could surely be even lower in cost. However, even at any finite [per-unit] cost of pennies, or fractions of pennies, objects comprising 10^6 components or more start to have significant cost. By reducing the complexity of the subunits to an absolute minimum, one can reconsider logic implemented by mechanical, chemical, or similar means. Babbage's revenge! At the level of just 5-6 states per subunit, one can start to imagine mechanical or chemical finite state machines that make up the micro- (or potentially nano-) scale subunits for replicating more complex machines."

3.29 Self-Replicating Robotic Lunar Factory (SRRLF) (2003-2004)

Two private groups[1313] devoted to space colonization have undertaken the design of a self-replicating robotic lunar factory (SRRLF) with the ultimate objective of constructing several operative space manned stations having room for thousands of inhabitants in a 3-4 decade timeframe. The lunar factory replicator, besides replicating itself, will also produce an additional quantity of materials for export to Earth or lunar orbit. This ongoing volunteer open-source design effort is explicitly intended as an update and extension of the 1980 NASA replicating lunar factory study (Section 3.13.2) and thus the two designs have many similarities.

Valenti Pineda,[1314] an industrial robotics and automation engineer in Spain who is leading the technical design effort, notes that the technology needed to transport a SRRLF to the Moon was proven well over 30 years ago. The technology in robotics and automation needed to successfully operate a prototype lunar factory simulator on Earth is now powerful enough to build it and to produce the required software and know-how to operate the factory on the Moon. "My estimate is a SRRLF can be designed using current robotic technology with the target of reaching 99% self-replication by weight, then begin the battle of reducing the remaining 1% that would be difficult to self-replicate using current technology," says Pineda.[1314] "In any event, this 1% consists of small and relatively lightweight components and wouldn't be prohibitively expensive to import from Earth — e.g., control electronics, communication equipment, lubricants, dopant for solar cell production, etc."

The factory is being designed so as to make robotic work as reliable and easy as possible. For example, to make robot transportation and locomotion easy and reliable, robots engaged in lunar soil mining operations will run on wheeled structures adaptable to lunar soil and will have autonomous AI navigation (Figure 3.88). Robots that must run inside the factory are mounted on motor boxes and move along an internal railroad (Figure 3.89), with navigation determined by a single-dimensional positional key. The factory consists of several modules partially buried in the lunar soil and connected at factory soil level by railroads where the displacement along railroads from any factory floor location to any other floor location is known to robots and payloads. The floor of the lunar factory is made of sintered lunar regolith. The modules of the first factory are delivered from Earth and assembled at a site previously founded

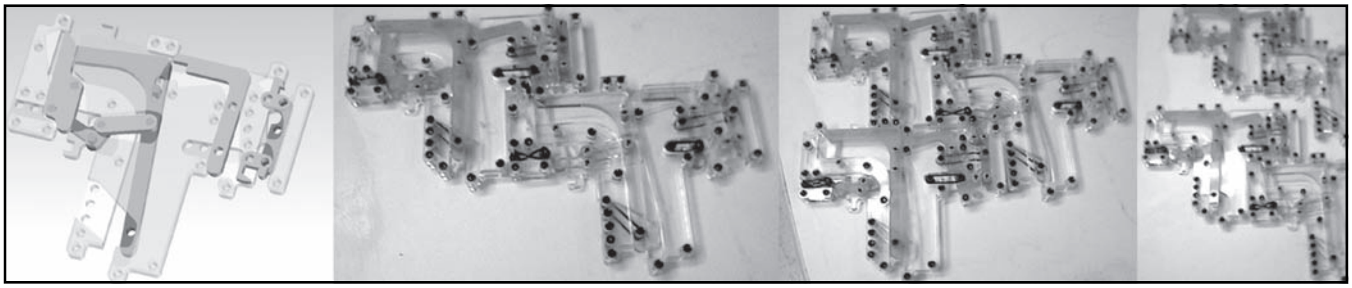


Figure 3.87. Physical implementation of Griffith self-replicating wire. (image courtesy of Saul Griffith[1312])

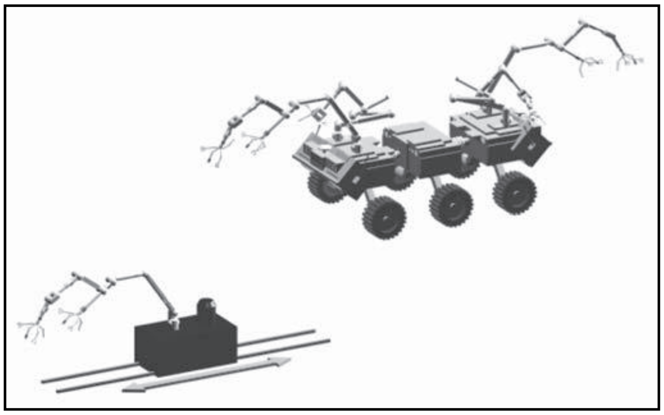


Figure 3.88. Types of mobile robots at the SRRLF. Autonomous AI navigating wheeled robots (top right) are used for lunar terrain investigation and raw materials mining; motor boxes on rails for single-dimension navigation are used inside the lunar factory (bottom left). (images courtesy of Valenti Pineda[1314] and The Preparation[1313])

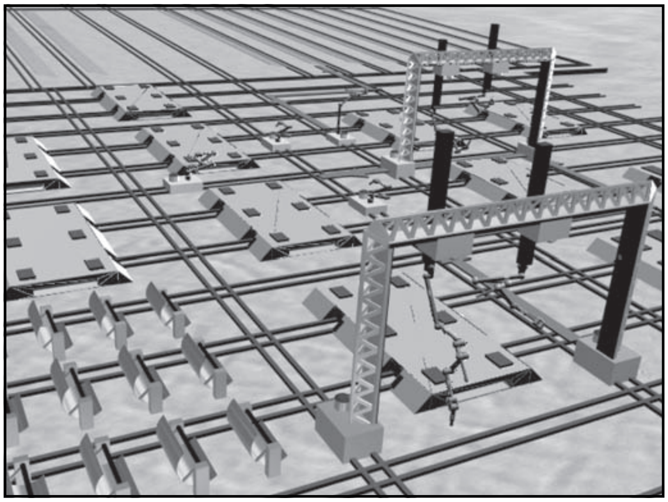


Figure 3.89. Perspective view of possible motions of robots and gantries on the SRRLF factory floor. (image courtesy of Valenti Pineda[1314] and The Preparation[1313])

and excavated by robots. Multifunctional robots are the workforce in the factory for all required industrial tasks such as welding, visual inspection, assembling, and so forth. The robots must be designed not only to carry out these tasks but must also be maintained, repaired, mounted and replicated by themselves using the least possible number of different types of parts.

The phases for SRRLF construction are as follows: (1) selection of lunar landing site; (2) excavation, founding and factory floor construction by assembly of sintered regolith blocks and rails; (3) deployment and assembly of factory equipment; and finally (4) factory startup. As indicated by the flowchart in Figure 3.90, the factory consists of the following processing modules, listed in order of operation:

- Autonomous wheeled robots for lunar soil mining deposit excavated materials in light trucks that run along the central railroad to the factory.
- Raw materials go to solar ovens and materials separators.
- Preprocessed materials go to chemical processing sector where primary materials will be obtained; unusable portions of these materials go to the factory dump.
- Primary materials move to the fabrication sector to be turned into useful mechanical and electrical pieces.
- Fabricated pieces move to the assembly sector where subassemblies are made and inspected for quality before being sent on for final assembly.
- Logistical planning requires the use of specific sites for storage, recycling, repair, and maintenance of pieces and equipment inside the factory.

Two central rails will be continually enlarged by construction using processed material within the factory, making it possible for

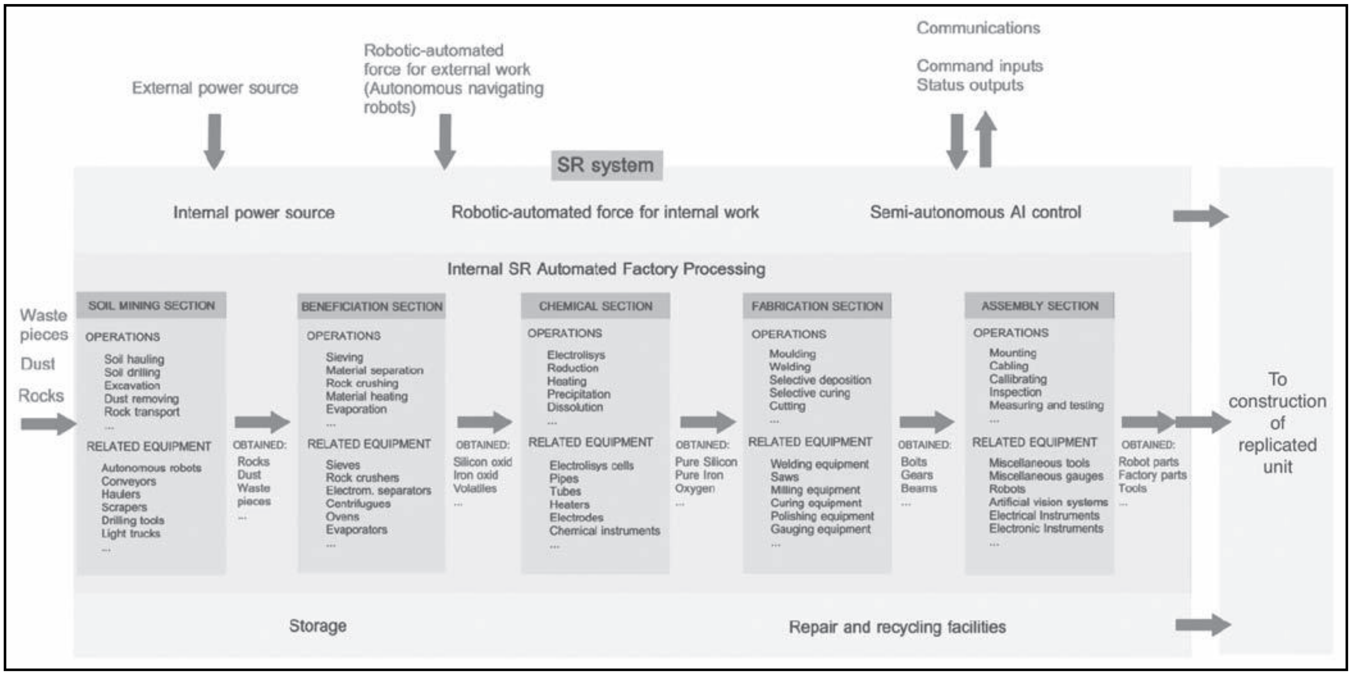


Figure 3.90. Functional flowchart of the SRRLF factory in operation. (image courtesy of Valenti Pineda[1314] and The Preparation[1313])

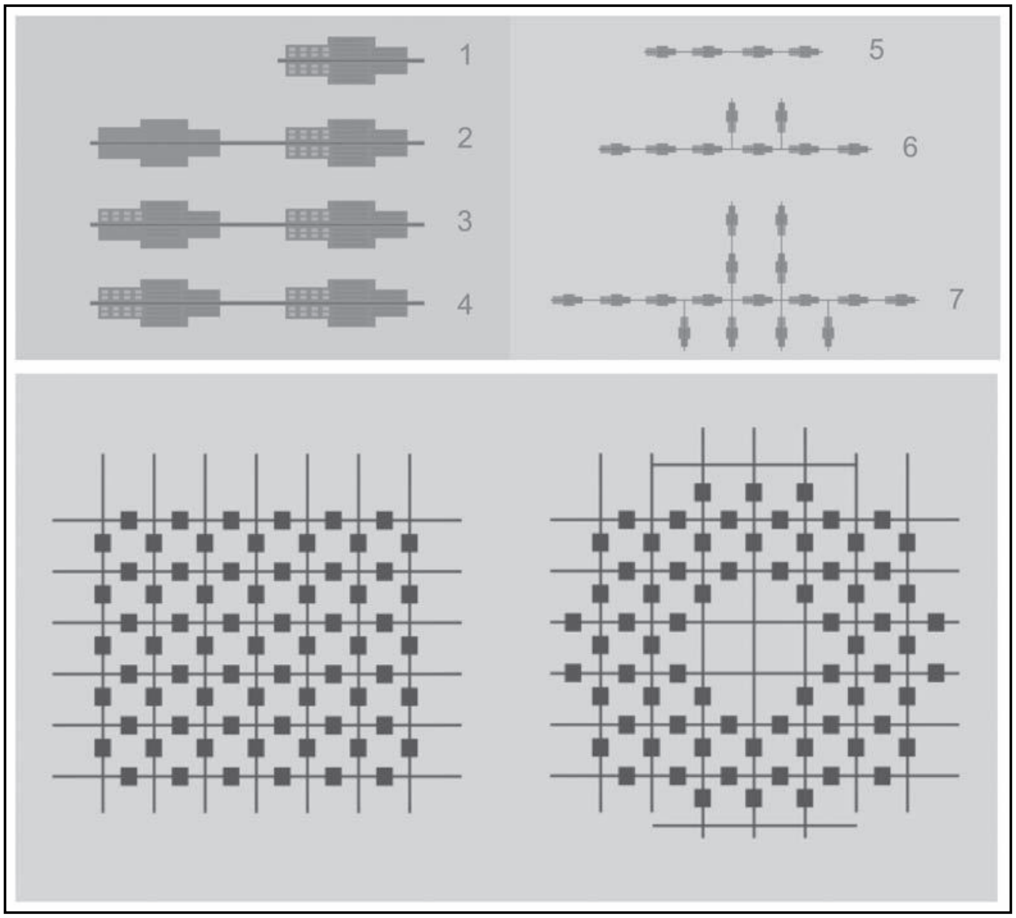


Figure 3.91. SRRLF replication pattern across the lunar surface. (images courtesy of Valenti Pineda[1314] and The Preparation[1313])

robots to travel faster to distant mining sites and to deliver mined materials back to the factory. Separate replicated factories are connected among themselves by these rails. In the progressive replication pattern illustrated in Figure 3.91, the first factory (1) constructs the central rail and foundation of the second factory, then (2) installs early modules and (3) solar power arrays, and finally the rest of the components of the second factory (4). (Precise distances between daughter factories may vary depending on materials needs, site details, etc.) The first two SRRLFs then generate one daughter each (5); then all four replicate to make 8 units (6), and then produce a total of 16 units after the next replicative cycle (7). Once the number of replicators is large enough and the earliest mining sites have been exhausted, sending raw materials to the earliest factories may delay replication so it is better to dismount the robotic modules from these early factories and transport them to peripheral mining sites, leaving the vacated interior spaces for future human settlements.

Lunar replicators continue making a grid (top) of railroad-connected factories on the lunar surface. When materials are exhausted inside the grid (bottom left), factory modules are moved outward to the periphery of the grid (bottom right) to regain ready access to more raw materials, with empty places used for future human settlements.

CHAPTER 4

Microscale and Molecular Kinematic Machine Replicators

There is substantial interest in examining the feasibility of molecular assemblers as manufacturing systems for nanotechnology. Perhaps the most obvious proof of principle that molecular-scale self-replication is possible at all is the example of biology. Among all "autopoietic" systems (Section 5.1), living things represent a large class of replicators that have been "reduced to practice" in working physical systems, at replicator size scales ranging from tens of nanometers (viruses) to tens of meters (whales). The techniques of biotechnology are regularly used to alter both structure and function of cellular replicators, producing biological kinematic replicators altered to specifications determined by human bioengineers. The first references to "molecular automata" began appearing in the early 1960s.[1315,1316] There are many individual molecules known to be capable of self-replication, and both self-assembly and positional assembly are employed inside living cells as they replicate. Many nonbiological molecular or microscale replicators have been suggested, including several proposals for replicators using molecular-scale positional assembly to be made of extremely durable nonbiological materials such as diamond. These latter replicators are called molecular assemblers, an important subject of this book.

The authors are most interested in the subject of nanomechanical replicators. As noted by Aristides Requicha, Director of the Laboratory for Molecular Robotics at the University of Southern California, in 2003:[1317] "Construction of nanorobots and NEMS [nanoelectromechanical systems] is still in its infancy. However, progress in exploiting biological motors and in developing artificial nanomachines has been rapid over the last few years, and the first (and fairly primitive) nanorobots are likely to emerge from research labs within the next five to ten years. Building and testing of nanodevices, and coupling of nanodevices to build integrated systems that can be interfaced with the micro/macro world continue to be major challenges."

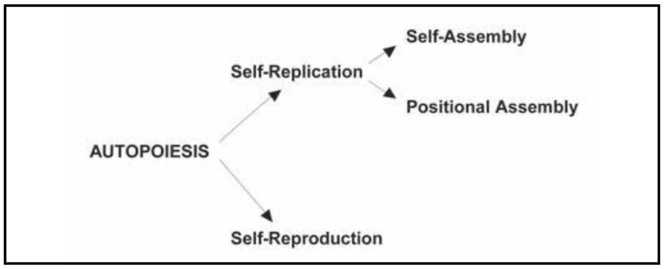


Figure 4.1. Clarification of one important aspect of the replicator design space.

In this Chapter, we review a variety of microscale and molecular kinematic replicators that have been proposed, or have been discovered or realized in physical implementations. However, before proceeding further it is necessary to clearly distinguish three terms (Figure 4.1) that are frequently confused:

Self-replication: the end result of a virtual or physical construction* process in which an object (called a "replicator") makes as true a copy of itself as possible.[705] Depending upon the nature of the object and the environment in which it resides, many different construction processes might be employed to achieve this final result. One such construction process (resulting in self-replication) might be self-assembly. Another such construction process (also resulting in self-replication) might be positional assembly. ("Self-replication" is to be distinguished from "self-reproduction", a process in which an object makes imprecise copies of itself that may incorporate heritable variation of sufficient magnitude to allow natural selection and evolution to occur).** [200,2430]

"Replication" is also sometimes distinguished from "self-replication" in that the former describes a general ability to copy some range of physical structures[1318] while the latter may describe the more narrow ability of a system to copy its own physical structure. These terms are used almost interchangeably in this book because analysis reveals that this distinction actually extends along several different dimensions of the replicator design space (e.g.,

---

** In traditional engineering, "construction" refers to the manufacture of physical objects using the techniques of fabrication, assembly, or both. "Fabrication" customarily refers to materials transformation processes involving the alteration of interatomic strong (covalent or ionic) bonds within a single component (e.g., chemical, phase, or deformative transformations), whereas "assembly" customarily refers to the spatial rearrangement of fabricated components or "parts" that involve no alteration of interatomic strong bonds within the components (e.g., pressure-fitting, snap-fitting, fastening, weaving, complementary interlocks) but may involve altering atomic bonds between components (e.g., adhesives, joining of unterminated diamond surfaces). When components shrink to the size of atoms or molecules, the distinction between fabrication and assembly disappears. For convenience we choose to label such transformative processes as assembly, e.g., "molecular assembly," though "molecular fabrication" would be equally apt.*

*** There is some subtle dissent from this approach. For example, Gerald Joyce[601] is of the opinion that "most biochemists would disagree with the distinction that is being made between 'self-replication' and 'self-reproduction'. Instead they would distinguish between 'error-free self-replication' and 'error-prone self-replication'."*

dimensions I6, I7, I16 and J6; Section 5.1.9) and thus may more easily lead to confusion than enlightenment; hence the distinction seems not particularly useful in normal discourse.

For instance, the word "self" may refer to the thing being made — that is, to the fact that the entity in question is making copies of its own physical structure, rather than the physical structure of something entirely else, or even imperfect copies of itself. Or "self" may refer to the way a thing is being made — that is, the ability of an entity autonomously to make copies on its own without outside assistance, as opposed to some other replicating entity which can only replicate with the assistance of outside entities. This usage of "self" would then be synonymous with closure, with a "self-replicator" having 100% closure while an ordinary "replicator" would not. Since few replicating entities can have 100% closure in all dimensions (in time needing at least some materials, energy, or sensory or other information inputs from the environment), then few entities could be called "self" replicating in this usage. For example, human beings, requiring Vitamin C inputs from the environment, lack 100% materials closure and thus would be excluded.

Still others have tried to identify "self" replication with descriptive information closure only, or with process control information closure only, or with others of the many design dimensions of the replication space (Section 5.1.9). Rather than trying to burden the term "self" with some arbitrary meaning that is more likely to confuse than to inform, we feel it is best to treat the terms "self-replication" and "replication" as interchangeable, and direct readers who seek clarification and greater precision to our comprehensive replication design space analysis (Section 5.1.9), where said readers can then select whichever conceptual restrictions seem most appropriate under the circumstances. Similar comments pertain to the usage by some writers of "auto-" in place of "self-".

Self-assembly: one of several construction processes by which self-replication may be achieved; an alternative to positional assembly. Self-assembly is a stochastic process wherein only the final state (the desired end configuration), and not the pathway taken to it, is specified.[1319] Molecular self-assembly is a strategy for nanofabrication that involves designing molecules and supramolecular entities so that shape- and charge-complementarity causes them to spontaneously aggregate into desired structures.[1326] "Self-assembly" thus refers to a process in which a construction occurs spontaneously and stochastically "by itself," but does not necessarily refer to a process in which a construction results in a duplication of a selfsame device. Indeed, the result of self-assembly is frequently a much larger compound object markedly different from the original smaller component objects that have self-assembled. Pier Luisi[1320] believes that the term "self-assembly" should be reserved "either to spontaneous processes, i.e., those under thermodynamic control; or those that are generated by the internal laws of the system (like the construction of an ant nest, determined by the inner genome of the species)." Self-assembly can also be defined as the reversible formation of a supramolecular structure (or complex) from two or more molecular components via one or more noncovalent interactions including electrostatic, H-bonds, or van der Waals interactions.

Whitesides[1321] notes that "self-assembly" has been deemed to include processes ranging from the non-covalent association of organic molecules in solution to the growth of semiconductor quantum dots on solid substrates, but prefers to limit the term to "processes that involve pre-existing components (separate or distinct parts of a disordered structure), are reversible, and can be controlled by proper design of the components."

Positional assembly: one of several construction processes by which self-replication may be achieved; an alternative to self-assembly. Positional assembly is a deterministic process in which the components used in a construction are held in known positions and are constrained to follow desired intermediate physical pathways throughout the entire construction sequence. (Like self-assembly, the final state or desired end configuration is also specified.) Positional assembly is useful whenever reacting structures might have prematurely reacted elsewhere if not positionally constrained. The use of highly reactive compounds permits a simple and direct synthetic process that provides greater flexibility and makes possible the synthesis of a much wider range of structures than is possible using self-assembly alone. (For example, attempts to reliably self-assemble highly reactive components, even if chemically distinct, must fail when those components collide with each other in undesired but still reactive conformations — although competing reaction barriers can increase the probability of correct assembly in some instances, most notably complementary DNA strands.) The result of positional assembly may be an object physically different from the original object that performed the positional assembly construction process, or it may be an object that is a close physical duplicate of the original object that performed the positional assembly construction process. A macroscale analog is the part-by-part assembly of automobiles on a robotic production line while maintaining continuous positional control[1322] of all parts and processes.

Before proceeding further, one additional point must be made. The last half of Chapter 4 presents a number of hypothetical designs for kinematic self-replicating machines which run considerably ahead of full experimental verification. There are justifiable and pragmatic concerns that "the principle has gotten so far ahead of the practice" that these theoretical designs may no longer be well-grounded in reality, or that as practice slogs along behind theory, technical issues might arise that could have significant impact on the details of these designs. While this is an important caution to bear in mind, still it seems unlikely that we will ever be able to build an assembler in the absence of a design for one. Trial designs are an important part of common engineering practice and are useful for uncovering previously hidden design flaws. It is also unlikely that a molecular assembler will soon be built if such construction is generally regarded as impossible within the engineering and scientific community. In the absence of an experimental ability to build a complete system today, it is nevertheless fruitful to examine a wide variety of intermediate designs to help identify components or processes that might be susceptible to near-term experimental or computational validation, with a view toward reducing the remaining uncertainties and unknowns involved in such designs. Concerned readers may wish to briefly detour to our extensive discussion of these issues in Chapter 6 before confronting the balance of Chapter 4.

4.1 Molecular Self-Assembly and Autocatalysis for Self-Replication

There is a wide range of different molecular systems that can self-assemble[1323,1324], and space does not permit more than a brief review here. Perhaps the best-known self-assembling molecular systems include those which form ordered monomolecular structures by the coordination of molecules to surfaces [1325], called self-assembled monolayers (SAMs) [1326-1328], self-assembling thin films,[1328-1330] Langmuir-Blodgett films,[1328,1331] self-assembling lipidic micelles and vesicles,[1332-1335] or self-organizing nanostructures.[1336,1337] In many of these systems, a single layer of molecules affixed to a surface allows both thickness and composition in the vertical axis to be adjusted to 0.1-nm by controlling the structure of the molecules comprising the monolayer, although control of in-plane dimensions to <20 nm remains difficult. Fluidic self-assembly of microscale parts,[1345-1351] nanoscale parts,[1357,1972] and the dynamics of Brownian self-assembly[1358] have also been described, and the theory of designable self-assembling molecular machine structures[1546,1565] and the computational modeling of self-assembly processes[1359] are beginning to be addressed.

A bench chemist would define autocatalysis (Section 4.1.6) very narrowly as the catalysis exhibited by a product of a reaction. Following a standard textbook definition, a catalyst accelerates a reaction while being neither consumed nor produced in the reaction. An autocatalyst, however, is a catalyst that is produced in a reaction. Upon production, an autocatalyst accelerates its own formation, initially leading to an exponential (more generally, nonlinear) increase in the number of autocatalytic molecules. A very simple example of an autocatalytic reaction is the hydrolysis of a carboxylic ester in "neutral" water: $RCO_2R' + H_2O \rightarrow RCO_2H + R'OH$. Ester hydrolysis is known to be catalyzed by acids. Since an acid (RCO_2H) is produced in the reaction, the product feeds back into its own synthesis. One may write: $RCO_2R' + RCO_2H + H_2O \rightarrow 2\ RCO_2H + R'OH$ to indicate that the process is autocatalytic.

Following Lehn's "instructed mixture" paradigm[1360] — in which large molecules can store more "information" than small molecules, and in which chemical information is "stored" as constitution (the network of bonds between atoms), configuration (the 3-D arrangement of bonds at "stereogenic" atoms), and long-living conformation (the 3-D orientation of atoms at bonds allowing for internal rotations) — self-replication via autocatalysis means autocatalysis in a bond-making reaction creating chemical information. The usual mechanism to transfer chemical information is templating: The template "instructs" its components in such a way that a specific bond is formed between the components. Templating is based on self-assembly, viz. the "docking" of components by noncovalent interactions.

Examples of chemical systems capable of templating and catalyzing their own synthesis — self-replicating systems — have begun to appear in the chemical literature over the last two decades,[1370-1374] starting with the first demonstration of a chemical self-replicating system by von Kiedrowski.[1373] Various template-dependent ligation systems have been devised to study the role of a template in binding and positioning complementary substrates for covalent bond formation.[1377-1381] These have included simple self-replicating systems of the form $A + B \rightarrow T$, where A and B are substrates that bind to a complementary template, T, and become joined to form a product molecule that is identical to the template,[1373-1376] so that the reaction product has the potential to direct additional reactions.[1372] The system is termed autocatalytic when the newly formed product is able to direct the assembly of additional product (template) molecules.

The self-replicating systems that have been studied through 2004 use template molecules composed of nucleic acids,[1366,1373,1375] peptides,[1384-1387] peptide nucleic acids[1388-1391] or nucleobase amino acids,[1392] and small organic compounds.[1620-1623] The nucleic acid-based systems rely on simple Watson-Crick pairing interactions between a short oligonucleotide template and two complementary oligonucleotide substrates.[1366,1373,1375] As described by Paul and Joyce,[1372] the substrates are bound at adjacent positions along the template and are joined through a reaction involving chemical groups at their opposed ends.[1372] Peptide-based self-replicating systems are similar, except that the components are oligopeptides that can form alpha-helices.[1372] The template is the hydrophobic face of an alpha-helix that interacts with the corresponding face of two peptide substrates.[1384-1387] Unlike nucleic acid systems, where the templating interactions involve all of the nucleotide subunits, peptide replication systems involve only a few amino acid residues in the helix-helix interactions.[1372] The remaining residues are responsible for maintaining the overall fold of the helix, demonstrating that the templating properties of a self-replicating system need not necessarily involve interactions with every residue in the polymer.[1372] Self-replicating systems based on organic compounds further generalize the notion of a template, as these systems are not based on a polymer but rather on a low molecular weight compound that presents a templating surface to bind the two substrates.[1620-1622]

In the following discussion we briefly review self-assembling peptides, porphyrins and nucleotides (Section 4.1.1), self-assembling crystalline solids (Section 4.1.2), self-assembling dendrimers (Section 4.1.3), self-assembling rotaxanes and catenanes (Section 4.1.4), self-assembly of mechanical parts and conformational switches (Section 4.1.5), and finally autocatalysis and autocatalytic networks (Section 4.1.6).

4.1.1 Self-Assembling Peptides, Porphyrins, Nucleotides and DNA

One approach using solid-phase peptide synthesis and a convergent self assembly process was employed by M.R. Ghadiri and colleagues,[1393-1398] who designed and synthesized a number of self-assembling peptide-based organic nanotubes using cyclic peptides with alternating D- and L-amino acids for the building blocks of the nanotubes. The alternating stereochemistry of the cyclic peptides allowed all the side chains of the amino acids to be pointing outwards which would not be possible in an ordinary all L-cyclic peptide. In this conformation, the amide backbone can H-bond in a direction perpendicular to the plane of the cyclic peptide. The stacking of two cyclic peptides forms an H-bonding network resembling an anti-parallel beta-sheet[1399] as is commonly found in natural proteins. The H-bonding lattice quickly propagates perpendicular to the plane of the cyclic peptide, forming a tubular microcrystalline structure with 0.75-nm pores, or, in another experiment, 1.3-nm pores.[1400] Another group of nanotubes was designed with a highly hydrophobic outer surface and a hydrophilic inner pore. These nanotubes were easily inserted into a lipid bilayer and have been shown to be highly efficient ion channels.[1397,1401] Nanotubes with slightly larger pores transport small molecules such as glucose as well.[1402] Stable flat nanodisks with diameters continuously (chemically) adjustable from 30-3000 nm have been self-assembled in surfactant solutions.[1403] Other groups have investigated self-assembling peptides to form nanotubes and nanovesicles.[1404-1406]

Yokoyama et al[1407] report the formation of surface-supported supramolecular structures whose size and spontaneous aggregation pattern are rationally controlled by tuning the selective and directional non-covalent interactions between individual substituted porphyrin molecule "molecular building blocks" adsorbed on a gold surface that form monomers, trimers, tetramers or extended wire-like structures. "We find that each structure corresponds in a predictable fashion to the geometric and chemical nature of the porphyrin substituents that mediate the interactions between individual adsorbed molecules," note the researchers. "Our findings suggest that careful placement of functional groups that are able to participate in directed non-covalent interactions will allow the rational design and construction of a wide range of supramolecular architectures absorbed to surfaces, [potentially enabling] the realization of molecule-based miniature devices with advanced functions." Crossley's group[1408] is also studying self-replication and templated synthesis of porphyrin systems.[1409]

Fenniri et al[1410-1413] have used the heteroaromatic bicyclic base G^C which possesses the Watson-Crick donor-donor-acceptor of guanine (G) and acceptor-acceptor-donor of cytosine (C) at a fixed 60° relative angle, to achieve the self-assembly of helical rosette nanotubes which stack (six per hexagonal ring) only in the correct orientation because they are hydrophobic on

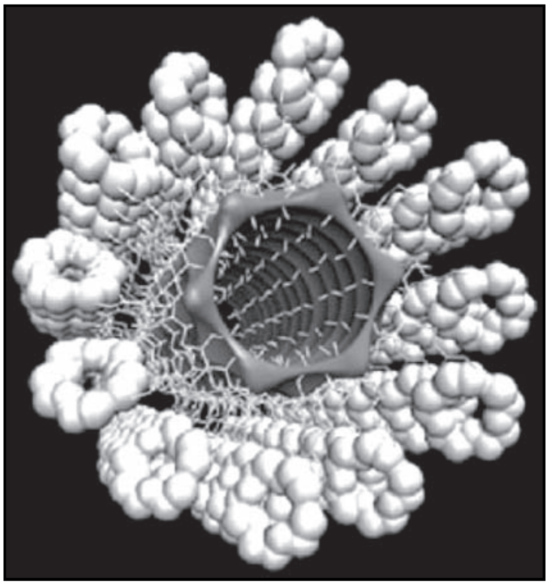


Figure 4.2. Top view of a self-assembled G^C rosette nanotube conjugated to benzo-18-crown-6. (courtesy of Fenniri et al[1411])

the inside and hydrophilic on the outside (Figure 4.2). "Because of the disymmetry of its hydrogen bonding arrays, their spatial arrangement, and the hydrophobic character of the bicyclic system, G^C undergoes a hierarchical self-assembly process under physiological conditions to form a six-membered supermacrocycle maintained by 18 H bonds (rosette). The resulting and substantially more hydrophobic aggregate then undergoes a second level of organization to produce a stack. The architecture thus generated defines an unoccluded central pore running the length of the stack with tunable inner and outer diameters. The inner space is directly related to the distance separating the H-bonding arrays within the G^C motif, while the peripheral diameter and its chemistry are dictated by the choice of the functional groups conjugated to this motif." Dendrimeric oligonucleotides as stable nanostructures have also been investigated by others.[1414]

The ideas behind self-assembled DNA nanotechnology have been around since 1980,[1438] but activity in this field accelerated in the 1990s after numerous experimental difficulties were surmounted. Horn and Urdea[1415] reported branched and forked DNA polymers. Niemeyer[1416] and Smith[1417,1452] suggested using self-assembled DNA as an early material for molecular nanotechnology. Damha[1418,1419] synthesized V-shaped and Y-shaped branched RNA molecules, branching RNA dendrimers with "forked" and "lariat" shaped RNA intermediates,[1420] and even trihelical DNA.[1421] Henderson and coworkers[1422-1425] designed a simple DNA decamer that can form an extended linear staggered quadruplex array reaching lengths of >1000 nm, and have made branched oligonucleotides that template the synthesis of their branched "G-wires"; depending on the ratio of linear to branched building blocks, extensive DNA arrays with differing connectivities but irregular interstices can be created.[1426] Von Kiedrowski's group[1363,1426-1428] has generated 3-D nanoobjects using trisoligonucleotides with covalent junctions whose self-assembly leads to noncovalent objects, which can then be selectively replicated using an electrophoretic process called eSPREAD.[1427,1428] Reif's group[1431] has produced self-assembled DNA-based nanotubes, and various self-assembled DNA-based dendrimers have been produced.[1432,1433]

Some of the most intensive and sustained work on three-dimensional engineered DNA structures has taken place in Nadrian Seeman's laboratory[1440-1450] in the New York University Department of Chemistry. Seeman originally conceived the idea of rigid 3-D DNA structures in the early 1980s[1438,1458] while examining DNA strands that had arranged themselves into unusual four-armed Holliday junctions.[1459] Seeman recognized that DNA had many advantages as a construction material for nanomechanical structures.[1444] First, each double-strand DNA with a single-strand overhang has a "sticky end," so the intermolecular interaction between two strands with sticky ends is readily programmed (due to base-pair specificity) and reliably predicted, and the local structure at the interface is known (sticky ends associate to form B-DNA). Second, arbitrary sequences are readily manufactured using conventional biotechnological techniques. Third, DNA can be manipulated and modified by a large variety of enzymes, including DNA ligase, restriction endonucleases, kinases and exonucleases. Fourth, DNA is a stiff polymer in 1-3 turn lengths[1460] and has an external code that can be read by proteins and nucleic acids.[1461]

During the 1980s, Seeman worked to develop strands of DNA that would zip themselves up into more and more complex shapes. Seeman made junctions with five and six arms, then squares,[1462] stick-figure cubes comprised of 480 nucleotides,[1440] and a truncated octahedron containing 2550 nucleotides and a molecular weight of ~790,000 daltons.[1443] The cubes were synthesized in solution, but Seeman switched to a solid-support-based methodology[1463] in 1992, greatly improving control by allowing construction of one edge at a time and isolating the growing objects from one another, allowing massively parallel self-assembly of objects with far greater control of the synthesis sequence. By the mid-1990s, most Platonic (tetrahedron, cube, octahedron, dodecahedron, and icosahedron), Archimedean (e.g., truncated Platonics, semiregular prisms and prismoids, cuboctahedron, etc.), Catalan (linked rings and complex knots), and irregular polyhedra could be constructed as nanoscale DNA stick figures.[1141,1151]

Seeman's DNA strands that formed the frame figures were strong enough to serve as girders in a molecular framework, but the junctions were too floppy. In 1993 Seeman discovered the more rigid antiparallel DNA "double crossover" motif,[1464] which in 1996 he used to design and build a stiff double junction to keep his structures from sagging.[1465] The next goal was to bring together a large number of stick figures to form large arrays of cage-shaped DNA crystals[1437] that could then be used as frameworks for the assembly of other molecules into pre-established patterns. These DNA molecules, including the newer "triple crossover" motifs,[1446] would serve as the scaffolding upon which new materials having precise molecular structure could be assembled.[1447-1449] Seeman's DNA nanoconstruction work has more recently began progressing toward DNA-based kinematic nanodevices (Section 4.5).

In 2004, Shih et al[1466,1467] at the Scripps Research Institute synthesized a single-stranded 1669-nucleotide DNA molecule that self-folds into a hollow octahedral structure ~22 nm in diameter in the presence of five 40-nucleotide synthetic oligodeoxynucleotides by a simple denaturation-renaturation process involving heating and a series of cooling steps (Figure 4.3). The central cavity can hold a sphere 14 nm in diameter, which would include fullerenes up to ~$C_{9,200}$ in size; the triangular openings on each face can admit spheres up to 8 nm (~$C_{2,900}$) in outside diameter. The base-pair sequence of individual struts is not repeated in a given octahedron, so each strut is uniquely addressable by the appropriate sequence-specific DNA binder.[1466] Unlike other DNA that forms three-dimensional objects, Shih's molecules can be readily copied by polymerases, hence is clonable. "Building complex three-dimensional DNA wireframes directly from synthetic oligonucleotides (as has been done in the past) is a very time-consuming and inefficient process, and thus not practical for many applications," said Shih in a February 2004

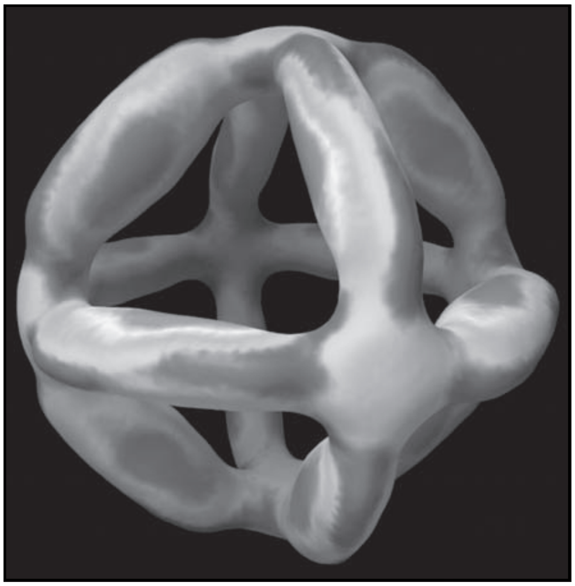


Figure 4.3. Structure of 1.7-kilobase single-stranded nanoscale self-folding DNA octahedron ~22 nm in diameter, using false-color visualization exhibiting the electron density of the object.[1466,1467] (courtesy of Gerald F. Joyce and Scripps Research Institute)

interview.[1467] "Polymerases could also facilitate the discovery of novel single strand encoded DNA molecular machines through the procedure known as directed molecular evolution. Directed evolution could be used for attempts to develop complex mechanical behavior from DNA loops organized by an octahedron scaffold. This could lead to custom molecular machines reminiscent of those found in nature — for example, molecular assemblers and disassemblers such as chaperones or polymerase clamp loaders. Directed evolution has already been used successfully to discover static and even allosterically controlled catalysts. It would be a great feat to evolve more complicated molecular machines, and amplifiable DNA nano-scaffolds could play a key role in meeting this challenge." Wengel[3278] has also discussed using DNA building blocks for nanoconstruction.

4.1.2 Self-Assembling Crystalline Solids

Self-assembled crystalline solids such as zeolites[1471-1473] incompletely fill space, leaving substantial voids that may be occupied by solvent molecules or other guest molecules. Such occupation produces solid-state host-guest complexes known as clathrates (from the Latin clathratus, meaning "enclosed by the bars of a grating"). MacNicol and co-workers[1468] reported the first rationally designed clathrate host in 1978, but the first true de novo design of an organic clathrate was in 1991.[1469] This involved the formation of an extensive three-dimensional diamond-like porous lattice built from a single Tinkertoy-type subunit containing four tetrahedrally arrayed pyridone groups that acted as connectors to assemble the units together in a well-defined geometry. However, the crystal was held together only by weak hydrogen bonds and the links had a rotational degree of freedom, rendering the exact crystal molecular arrangement unpredictable.[1470] Engineered nanoporous molecular crystals can provide molecular-scale voids with controlled sizes, shapes, and embedded chemical environments at resolutions of 0.3-4.0 nm.[1473-1479]

Other self-assembling crystal structures have been described[1480-1482] including the crystal engineering of diamondoid networks,[1483] template-directed colloidal crystallization or colloidal epitaxy,[1484] organic templating to form crystalline zeolite-type structures with ordering lengths <3 nm,[1485] 3-D polymer channels with chemically functionalizable channel linings,[1486] silver nanowire arrays,[1487] and micromolding combined with templating and cooperative self-assembly of block copolymers to produce hierarchical ordering over discrete and tunable characteristic length scales of ~10 nm, ~100 nm, and ~1000 nm in a single body.[1488] Redl et al[1489] at IBM have created a self-assembling 3-D metamaterial with a repeating pattern made up of 11-nm diameter (~60,000-atom) magnetic iron oxide particles and 6-nm diameter (~3000-atom) semiconductor lead selenide particles. This demonstrates "a modular assembly method that will let us bring almost any materials together...[and] the ability to bring together complementary materials with an eye to creating materials with interesting custom properties." Of course, the simple process of crystallization can be viewed as an example of templated self-assembly.

Non-crystallographic polyhedral nano-clusters that are not able to grow but nevertheless have the potential to bifurcate, regroup, and even "self-replicate" have also been proposed.[1490]

4.1.3 Self-Assembling Dendrimers

Dendrimers,[1491-1499] also known as arborols or fractal polymers, are a well-known set of self-assembling structures[1500] that possibly could be used as tools to assist in the assembly of early nanomachines. Dendrimers are large regularly-branching macromolecules resembling fractal patterns, made by an iterative process in which small linear molecules are allowed to bind to each other at a certain number of sites along their length, building up branches upon branches with each iteration working outward from a core molecule having at least two chemically reactive arms, somewhat mimicking tree growth. Different core molecules or building-block chains produce macromolecules with different shapes, and the outer surface can be terminated with chemical groups of specific functionality, producing hundreds of differently-surfaced branched molecules[1501] that have already found use in medical research.[1502] Growth is regulated, so size can be accurately controlled — dendrimers are typically a few nanometers wide but have been constructed with masses exceeding a million protons (~10^5 atoms) and with diameters larger than 30 nm.

Convergent assembly of specified 6-mer dendrimers via trimerization of precursor dimer "parts" was demonstrated in 1999.[1503] Dendrimer self-assembly into lattices and other multidendrimeric structures has been studied both computationally[1504,1505] and experimentally.[1506-1509]

DNA-based dendrimers have already been mentioned in Section 4.1.1.

4.1.4 Self-Assembling Rotaxanes and Catenanes

Noncovalent self-assembly of molecular parts has also been demonstrated. For instance, Fraser Stoddart and colleagues[1510-1515] have extensively investigated the rotaxanes,[1516] nanoscale systems in which one molecular part is threaded through a hole or loop in another molecular part, and kept from unthreading by end-groups, like a ring trapped on a barbell. In one system, a ring-shaped molecule slides freely along a shaft-like chain molecule, moving back and forth between stations at either end with a frequency of ~500 Hz, making an oscillating "molecular shuttle".[1511] This shuttling behavior can be controlled by a series of different chemical, electrochemical, or photochemical external stimuli.[1513,1517] Using another approach, G. Wenz[1518] threaded ~120 molecular beads onto a single, long, poly-iminooligomethylene polymer chain, making a "molecular necklace." Other groups are pursuing related research[1519-1521] regarding [n]-rotaxanes[1522,1523] and pseudorotaxanes (mechanically-threaded molecules),[1524,1525] while still others are using the necklace technique as a means of, for example, self-assembling ~2 nm wide cyclodextrin nanotubes[1526] and more complex molecular machines.[1527]

Another interesting molecular system that can be made entirely by self-assembly is the catenanes,[1516] which have two or more closed rings joined like the links of a chain. The rings are mechanically linked — there are no covalent bonds between separate links. The first 2-catenane (2 linked rings) was constructed by Edel Wasserman of AT&T Bell Laboratories in 1960, using simple hydrocarbon rings; the first 3-catenane was synthesized in 1977. In 1994, Fraser Stoddart and David Amabilino constructed the first 5-catenane,[1528] having ~372 atoms, dubbed "olympiadane" because of its resemblance to the Olympic rings, and in 1997 the same group announced the first deterministically-ordered 7-ring heptacatenane;[1529] another group later reported the spontaneous self-assembly of a 10-component catenane.[1530] Much research on larger polymeric chains of linked rings (e.g., oligocatenanes[1531]), supramolecular "daisy chains",[1532,1533] fullerene-containing catenanes,[1534] protein-based catenanes,[1535] and supramolecular weaving[1536] is now in progress. The smallest 2-catenane constructed to date has dimensions 0.4 nm x 0.6 nm.[1537] Self-assembled mechanically-interlocked 2-dimensional[1538-1540] and 3-dimensional[1541,1542] "infinite" arrays of single molecular ringlike species are known. Interestingly, in 1998 it was discovered that many viral coats (which also self-assemble) appear to be a 2-dimensional "chain-mail" weave of mechanically-interlocked protein rings. For instance, the spherical bacteriophage HK97 capsid shell consists of exactly 72 interlinked protein rings, specifically 60 hexamers and 12 pentamers.[1543]

4.1.5 *Self-Assembly of Mechanical Parts and Conformational Switches*

Several attempts have been made to achieve self-assembly of small mechanical parts to avoid direct parts grasping.[1341-1345] Saitou[1546] gives a simple example of "sequential random bin picking" in which a process of sequential mating of a random pair of parts drawn from a parts bin which initially contains a random assortment of parts can produce the mating of a desired pair of parts (Figure 4.4). It is already known that self-assembling molecular systems can be made to self-replicate if the components have sufficient complexity. An example in biology is offered by the bacteriophages (Section 4.3.3), viruses that infect and commandeer a bacterial cell's replication mechanism to synthesize their own component molecules such as nucleic acids and proteins.[1547,1548] Spontaneous self-assembly of the component viral proteins then occurs which produces hundreds of virus offspring in the host cell. While new viruses are formed via self-assembly of randomly arranged and randomly moving component protein molecules, the various component molecules do not associate with one another at random during the assembly process but rather associate in a definite sequence. Biologists believe that conformational switches in protein molecules facilitate this sequential self-assembly of bacteriophages. In a protein molecule with several bond sites, a conformational switch causes the formation of a bond at one site to change the conformation of another bond site. As a result, a conformational change which occurs during one assembly step provides the essential substrate for assembly at the next step.[1694] Smith[1456] has described a self-assembled fluorescent conformational switch using DNA scaffolds containing several targeted proteins.

Griffith[1544] also complains that existing self-assembling systems are "essentially meso- or macro-scale versions of crystallization"* and suggests expanding the toolbox of self-assembly by including dynamic components that emulate enzymatic allostery. Figure 4.5 shows Griffith's "mechanical enzyme" analog — a 2-bit mechanical state machine that programmatically self-assembles while floating at an interface between water and poly-fluorodecalin. The mechanical state machine has a mechanical flexure that acts as the 'switch' in the state machine, making a mechanical allosteric enzyme. "The problem in designing self-assembling components is to avoid undesirable metastable states, and to make the desired assembled geometries the lowest energy conformations of the system," Griffith observes. For example, "you will observe in Figure 4.5 that there are no straight edges on the components to avoid local energy minima on their collision." Griffith[1312] explains further: "The key in designing such systems is that the parts must fall through a cascade of increasingly lower energy states, each corresponding to one of the logical states desired. The difficulty comes in designing a system with those energy troughs. One particularly difficult aspect is that one must not only design for the desired states, but considering that all components are free to interact in solution, one must design the non-desirable interactions to have very low binding energy such that they will not stick permanently. Note that this is a simple 3-component, 2-state system. This quickly becomes an incredibly difficult task as the number of states and components in the system increases. One must take solace in the fact that biology had billions of years to evolve many non-competing allosteric state machines and uses three dimensions, not just two." Griffith notes that he is "making progress on a 3-state system, however it is a problem of increasing difficulty, and as more component types are added to a

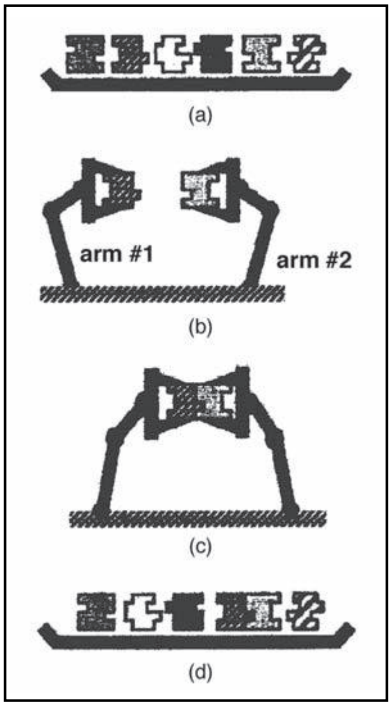


Figure 4.4. Self-assembly of parts using sequential random bin-picking.[1546] **Step (a):** The parts (possibly assemblies) are randomly arranged in the parts bin. **Step (b):** Arm #1 randomly picks up a part (possibly an assembly) from the bin. Then arm #2 randomly picks up another part (possibly an assembly) from the bin. **Step (c):** The two parts are pushed against each other, possibly forming an assembly. **Step (d):** The parts are returned to the bin, possibly as an assembly. (courtesy of K. Saitou)

---

* *A simple form of surface-tension-driven fluidic self-assembly has been illustrated with LEGO® blocks, which upon agitation form a square pattern while floating on water.*[1545]

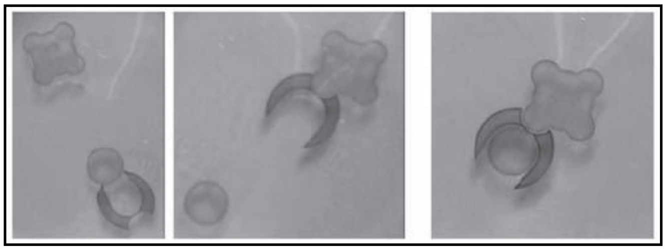


Figure 4.5. Griffith's mechanical allosteric enzyme — the allosteric horseshoe-shaped component is "opened" or activated when the 4-lobed "catalyst" part binds its functional site, the parts interacting due to meniscus forces; the bound circular part can only fit into the horseshoe once the catalyst is bound. (courtesy of Saul Griffith[1312,1544])

system the challenge is to avoid any undesirable local energy minima" — necessitating the development of energy vs. orientation modeling tools.[1544] He has also set a goal of finding an analogy to protein folding that will allow the folding of linear strings of mechanical parts into 2-D and 3-D structures which are voidless space-filling final objects.[1312] (See Section 3.28.)

The programming of engineered sequences of such conformational switches can allow the self-assembly of quite complicated mechanical structures. Saitou[1546-1551] has presented a model of self-assembling systems in which assembly instructions are written as conformational switches — local rules that specify conformational changes of a component. The model is a self-assembling automaton explicitly inspired[1546] by the Penrose[683] self-replicating blocks (Section 3.3) and by Hosokawa's self-assembling triangular parts with embedded switches.[1552] It is defined as a sequential rule-based machine that operates on one-dimensional strings of symbols. An algorithm is provided for constructing a self-assembling automaton which self-assembles a one-dimensional string of distinct symbols in a particular subassembly sequence. Classes of self-assembling automata are then defined based on classes of subassembly sequences in which the components self-assemble. For each class of subassembly sequence, the minimum number of conformations is provided which is necessary to encode subassembly sequences in the class. Finally, it is shown that three conformations for each component are enough to encode any subassembly sequence of a one-dimensional assembly of distinct components, having arbitrary length. Saitou claims[1546] his model of self-assembling automata can also be applied to self-assembly in 2- or 3-dimensions (in particular, to "the assembly of micro- to mesoscale components for microelectronic applications,") an extension which might eventually permit the design of physical systems capable of self-replication via self-assembly.

Programmable self-assembly has also been examined by Nagpal[1553] who asked how one might achieve a particular global shape or pattern from the local interactions of vast numbers of parts, in a robust and decentralized way, and what the appropriate local and global programming paradigms for engineering such systems might be. Nagpal presented "a language for instructing a sheet of identically-programmed, flexible, autonomous cells to assemble themselves into a predetermined global shape. A wide variety of global shapes and patterns can be synthesized, using only local interactions between identically-programmed cells. The global shape is described as a folding construction on a continuous sheet, using a language based on Huzita's axioms of origami. The program executed by a cell is automatically compiled from the global description, which is in contrast to approaches based on cellular automata and evolution. The cell program is inspired by developmental biology and is composed from a small set of primitives. The cell programs do not rely on regular cell placement, global coordinates, unique global identifiers, or synchronous operation, and are robust in the face of a small amount of random cell death." Saul Griffith's related work on programmatic self-assembling systems[1544] has been mentioned earlier, and the work of Hogg et al[1554] and DeHon et al[1555] should also be mentioned in this context.

Guided[1556-1564] or directed[2163-2167] self-assembly has become a growing research area. Hogg[1565] has also examined the designability of self-assembled structures, Yeh and Smith[1345] have described a process of fluidic self-assembly of optoelectronic devices, Rothemund and Winfree[1566] have described a tile assembly model for pseudocrystalline self-assembly, and Breivik[1567] has designed and patented a set of self-replicating physical polymers. Gracias et al[1568] have impressed electrical circuits including LEDs on the surfaces of copper-polyimide truncated octahedra each ~1 mm in diameter, then induced these octahedra to self-assemble into specified 3-D electrical networks of up to 12 devices by co-melting opposing solder spots. (Gracias notes that hierarchical self-assembly[1569] and shape-selective self-assembly using lock-and-key structures[1570-1573] "offer more sophisticated strategies for the fabrication of asymmetrical networks incorporating more than one repeating unit.") Whitesides et al[1574-1579] first demonstrated capillary-force driven assembly of a simple circuit and other structures from millimeter-scale components, and also magnet-driven fluidic self-assembly[2336] and electrostatic self-assembly.[1580] Some of this work has since been extended to the microscale,[1346-1356] including "micro-origami",[2445-2448] "silicon origami",[1581,1582] and mesoscopic nucleic acid analogs.[1583]

As one final observation, Crane[1584] long ago considered the principles for the assembly of larger parts from smaller parts, and concluded that if imperfect units were cast aside during a hierarchical assembly process, then complex structures could be produced without requiring high accuracy at any step (see also Section 5.9.4).

4.1.6 Autocatalysis and Autocatalytic Networks

Autocatalysis — a process in which the product of a chemical reaction acts as a catalyst for that same reaction — is perhaps the simplest form of molecular self-replication. Small autocatalytic reactions have long been known, for example, the formation of the porphyrin ring system from formaldehyde and pyrrole in the presence of iron and peroxide, as described in 1969 by Calvin,[1585] and other purely chemical oscillating reactions (reaction-diffusion type replication) such as the well-known Belousov-Zhabotinsky reaction[1586-1590] (see Noyes' explanation of it[1591]), self-replicating spots and pulses[1593-1601] based on the Gray-Scott model,[1592] Turing patterns[1601-1609] inspired by Turing's theory of chemical spatial pattern formation,[1614] and other oscillating chemical systems.[1609-1613]

In 1986, von Kiedrowski[1373] initiated the experimental field of "self-replication in chemistry" with the first demonstration of a simple chemical self-replicating system. As summarized by chemist Philip Ball:[1615] "When DNA replicates in cells, enzymes unzip the double helix and build two new strands, one base at a time, using the exposed single strand as a template. In the 1980s, Leslie Orgel of the Salk Institute in San Diego, California, found a way to copy short single strands without enzymes. Individual base pairs could assemble on a template strand and link up into a complementary strand. In general you can't make two identical strands from one in a single step, however, because the new strand is complementary to, not identical to, the template. But in 1986, von Kiedrowski realized that you could get around this by choosing to copy a sequence whose complementary sequence is identical to the original when read backwards. In this way his team demonstrated enzyme-free replication of a six-base strand of

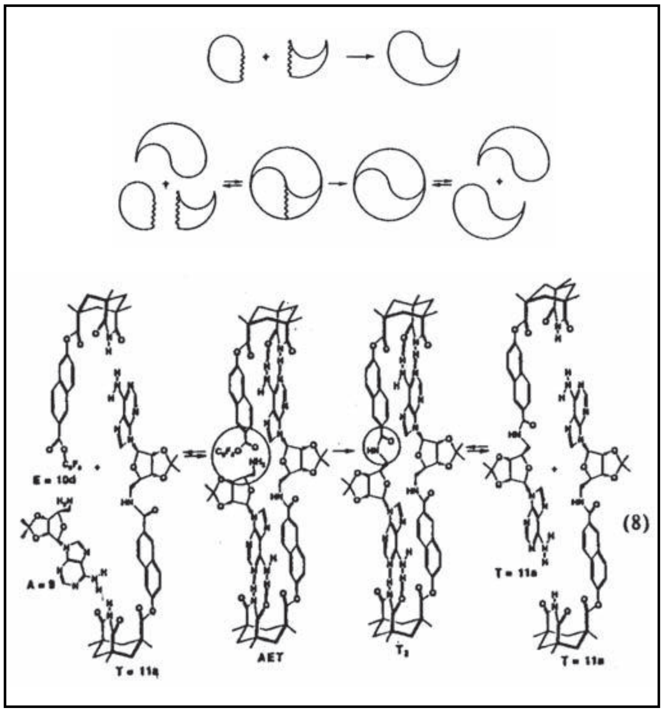


Figure 4.6. Rebek's self-complementary autocatalytic self-replicating molecules.[1617] (courtesy of JACS)

nucleic acid by using it as the template for assembling and linking together two three-base fragments." Thus all the basic design principles and all the basic findings were already published in 1986. The general scheme: $A + B + C \Rightarrow ABC \rightarrow C_2 \Rightarrow 2C$, where C is a self-complementary template, was general enough that it could be implemented using a variety of different molecules. Von Kiedrowski used short nucleic acids because he thought that if an RNA world ever existed, short pieces of nucleic acids must be able to replicate in the absence of enzymes.

In 1989, Rebek[1616-1620] reported the synthesis of supermolecules that could generate copies of themselves when placed in a sea of simpler molecular parts, with each component part consisting of up to a few dozen atoms, a process known as autocatalysis. Unlike the bipartite complementarities (e.g., plus and minus) found in the double strands of nucleic acids and in the complementary surfaces of certain peptides,[1624] Rebek's molecule exhibits self-complementarity or "templating" and thus provides a minimal system for replication. Illustrated schematically and as a molecular diagram in Figure 4.6, the sigmoid line represents the intermolecular contact between the two complementary and identical "AB" components. These units can be further broken along the jagged line into two different, yet complementary, pieces, "A" and "B". The cycle of self-replication is strongly reminiscent of the several mechanical block replicators described in Chapter 3. In this case, molecule AB (imide amide) catalyzes its own formation from its simpler components, A (aminoadenosine amine) and B (pentafluorophenyl imide ester), and this reaction then causes the two AB units to disengage, each ready to resume replication with the next partners — a close molecular analog of the simple Penrose block model (Section 3.3).

Molecular self-replication has continued to be studied and discussed by chemists.[1367-1370] There are many variants of autocatalytic networks, such as those investigated both experimentally and theoretically by Bagley et al,[1630-1632] Banzhaf et al,[1633-1638] Boerlijst and Hogeweg,[344,1639] Cousins et al,[1640] Farmer et al,[1628-1630] Ganti,[1641-1646] Ghadiri et al,[1382-1384] Hofbauer and Sigmund,[1647] Kauffman,[1625-1628] Rasmussen,[1648] Rossler,[1649] Schuster,[1650] Stadler et al,[1651-1656] Stassinopoulos et al,[1657,1658] Varetto,[1659] von Kiedrowski,[1361,1367,1660] and Wachtershauser.[1661] One well-developed example of autocatalytic networks is the theory of hypercycles[1662-1670] as first postulated by German biochemist Manfred Eigen.[1662,1663] Hypercycles are a connected network of functionally coupled, self-replicating chemical entities. Hypercycle reactions are interdependent, so no single reaction can be so successful that it drives out the other functions of a cycle — it is, in effect, a balanced ecosystem. Ghadiri[1385] reported a self-replicating peptide in 1996, showing that a 32-amino-acid peptide, folded into an alpha-helix and having a structure based on a region of the yeast transcription factor GCN4, can autocatalyze its own synthesis by accelerating the amino-bond condensation of 15- and 17-amino-acid fragments in solution. In 2001, a chiroselective peptide replicator was also demonstrated,[1671] and Ghadiri's laboratory has studied more complicated autocatalytic cycle networks.[1382-1384] It is unknown how complex such assembly cycles may be made, but Ghadiri has investigated a self-replicating 256-component molecular ecosystem incorporating ~32,000 possible binary interactions.[1672]

Self-ligating polynucleotide systems[1365-1367,1373] also are known, showing that autocatalytic systems based on specific ligation reactions are possible. For example, the simple and successful self-replicating molecular system described by von Kiedrowski[1373] uses a single-stranded DNA hexamer and its two trimer fragments, demonstrating (as with Ghadiri's replicating peptide) a polymer that catalyzes its own formation from two fragments. Template-based enzyme-free self-replication of nucleotide analogs,[1617] RNA,[1673] or longer DNA sequences[1674] has been shown. A polynucleotide system based on a ribozyme polymerase able sequentially to add the correct nucleotides (and thus copy itself) has also been proposed,[1627] and in 2001 Bartel et al[2054] synthesized a ribozyme (itself 189 nucleotides in length) that can make complementary copies of RNA strands up to 14 nucleotides long, regardless of sequence, with 98.9% accuracy. Paul and Joyce[1372] developed a self-replicating system based on a ribozyme that catalyzes the assembly of additional copies of itself through an RNA-catalyzed RNA ligation reaction — in particular, the R3C ligase ribozyme (size ~200 nucleotides or ~68,600 daltons) was redesigned so that it would ligate two substrates to generate an exact copy of itself, which then would behave in a similar manner. (The autocatalytic rate constant was 0.011 min^{-1} whereas the initial rate of reaction in the absence of pre-existing ribozyme was only 3.3×10^{-11} M-min^{-1}.) In principle, such autocatalytic polynucleotide systems[1361-1367,1373] could be combined with the elaborate DNA-based 3-dimensional structures, switches and motors produced by Nadrian Seeman's group,[1434-1437,1440-1446] Jaeger's tectoRNA geometrical figures,[1675-1678] or the protein-based 3-dimensional "nanohedra" of Padilla et al[1679] to create even more complex self-replicating molecular machines.

4.2 Ribosomes: Molecular Positional Assembly for Self-Replication

In 1981, Drexler[197] pointed out that complex devices resembling biomolecular motors, actuators, bearings, and structural components could be combined to build versatile molecular machine systems analogous to machine systems in the macroscopic world, and then concluded: "Development of the ability to design protein molecules will open a path to the fabrication of devices to complex atomic specifications, thus sidestepping obstacles facing conventional microtechnology. This path will involve construction of molecular machinery able to position reactive groups to atomic precision."

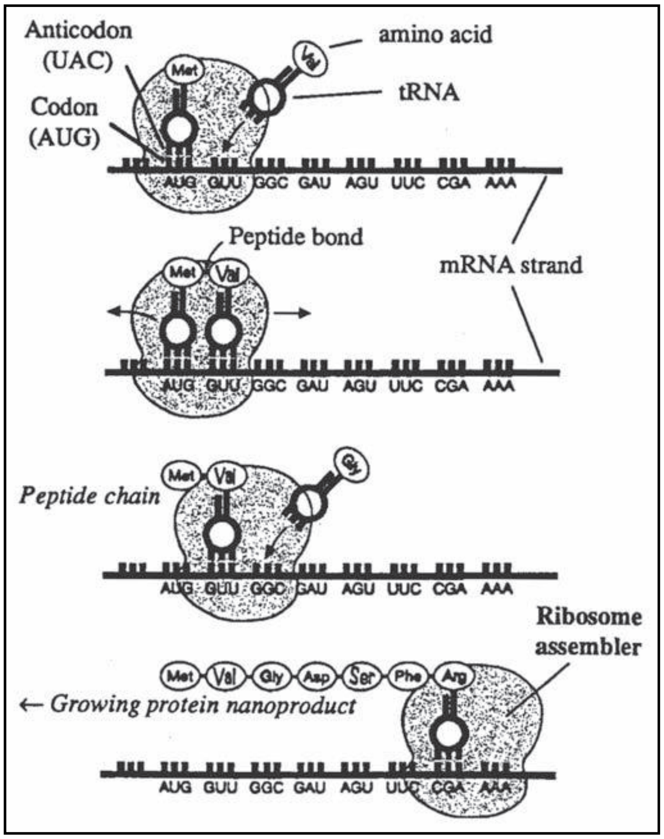


Figure 4.7. The ribosome acts as a programmable nanoscale assembler of protein nanoproducts.[228]

The best-known biological example of such molecular machinery is the ribosome, the only programmable nanoscale positional assembler currently in existence.* Numbering ~10^6-10^7 units per living eukaryotic cell and ~20,000 units per prokaryotic (bacterial) cell,[1693] ribosomes act as general-purpose factories building diverse varieties of proteins by bonding amino acids together in precise sequences under instructions provided by a strand of messenger RNA (mRNA) copied from the host DNA (Figure 4.7), with energy for ribosome movement along the mRNA tape provided by the hydrolysis of guanosine triphosphate (GTP).[1693] (The loading of transfer RNAs (tRNAs) with new amino acids by tRNA synthetase is powered by the conversion of ATP to AMP).[1680] Each ribosome is a compact ribonucleoprotein machine consisting of two subunits that fit snugly together, with each subunit consisting of numerous proteins associated with a long RNA molecule (rRNA). In mammalian cells, ribosomes are ~25 nm in diameter. The complete mammalian 80S ribosome unit has a total mass of 4.2 million daltons, including 2.8 million daltons for the large (~23 nm diameter) ribonucleoprotein 60S subunit containing 4998 bases and 49 proteins, and 1.4 million daltons for the small (~9 nm diameter) ribonucleoprotein 40S subunit containing 1874 bases and 33 proteins.[1693] The 80S unit is 60% rRNA by mass.[1693] Unlike other cellular polymerases, the ribosomal mechanism of action appears to depend almost entirely on the rRNA component; that is, ribosomes are giant ribozymes.[1681-1684]

Bacterial ribosomes (Figure 4.8) measuring ~20 nm in diameter have been the most extensively investigated.[1688] The complete bacterial 70S ribosome unit is 66% rRNA by mass and is formed by the association of the large 50S subunit and the small 30S subunit through a network of intermolecular bridges.[1689] The large 50S subunit contains one 23S rRNA molecule composed of 2904 nucleotide bases and one 5S rRNA molecule composed of 120 bases, both embedded in a framework of 31 structural proteins which are located mainly at the periphery. The small 30S subunit contains one 16S rRNA molecule composed of 1541 bases embedded in a framework of 21 similarly mostly peripheral structural proteins.[1690-1693]

The full crystal structures of the core components of this biological machine were mapped to 0.55 nm accuracy in 2001 and are available for our inspection.[1688,1696] Figure 4.9 shows the nucleotide base layout (top) and 3-D folded structure (bottom) of the 23S rRNA (I to VI) and the 5S rRNA comprising the large 50S subunit. Figure 4.10 shows the nucleotide base layout (left) and 3-D folded structure (right) of the 16S rRNA comprising the small 30S subunit. The core of the bacterial ribosome consists of 4565 "molecular parts" (nucleotide bases) of only four different "parts types" (the nucleotide bases A, C, G, and U), and the supporting protein structural framework of total mass ~0.85 MDa[1693] is constructed of 52 distinct proteins composed of ~6025

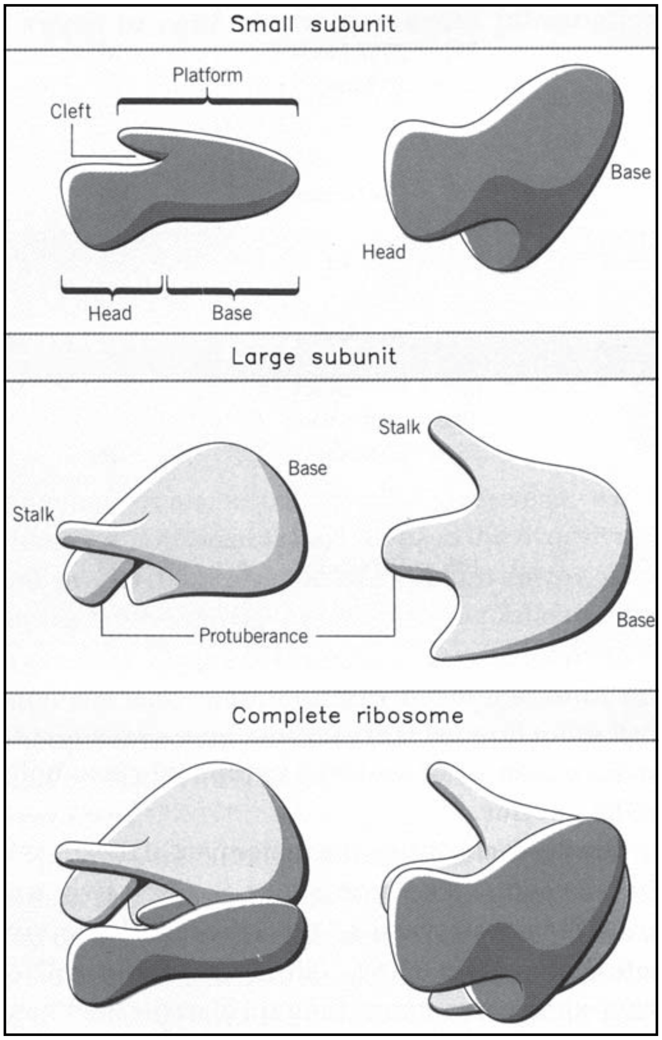


Figure 4.8. General 3-D topography of the bacterial ribosome: side (left) and bottom (right) views of the small 30S subunit (top), the large 50S subunit (middle), and the complete 70S ribosome unit (bottom). (from Genes V by Benjamin Lewin (1994), by permission of Oxford University Press www.oup.com[1693])

---

* There are three distinct types[1687] of ribosome — eubacterial, archaebacterial and eukaryotic — and multiple subvarieties among the ~10^8 different species on Earth.

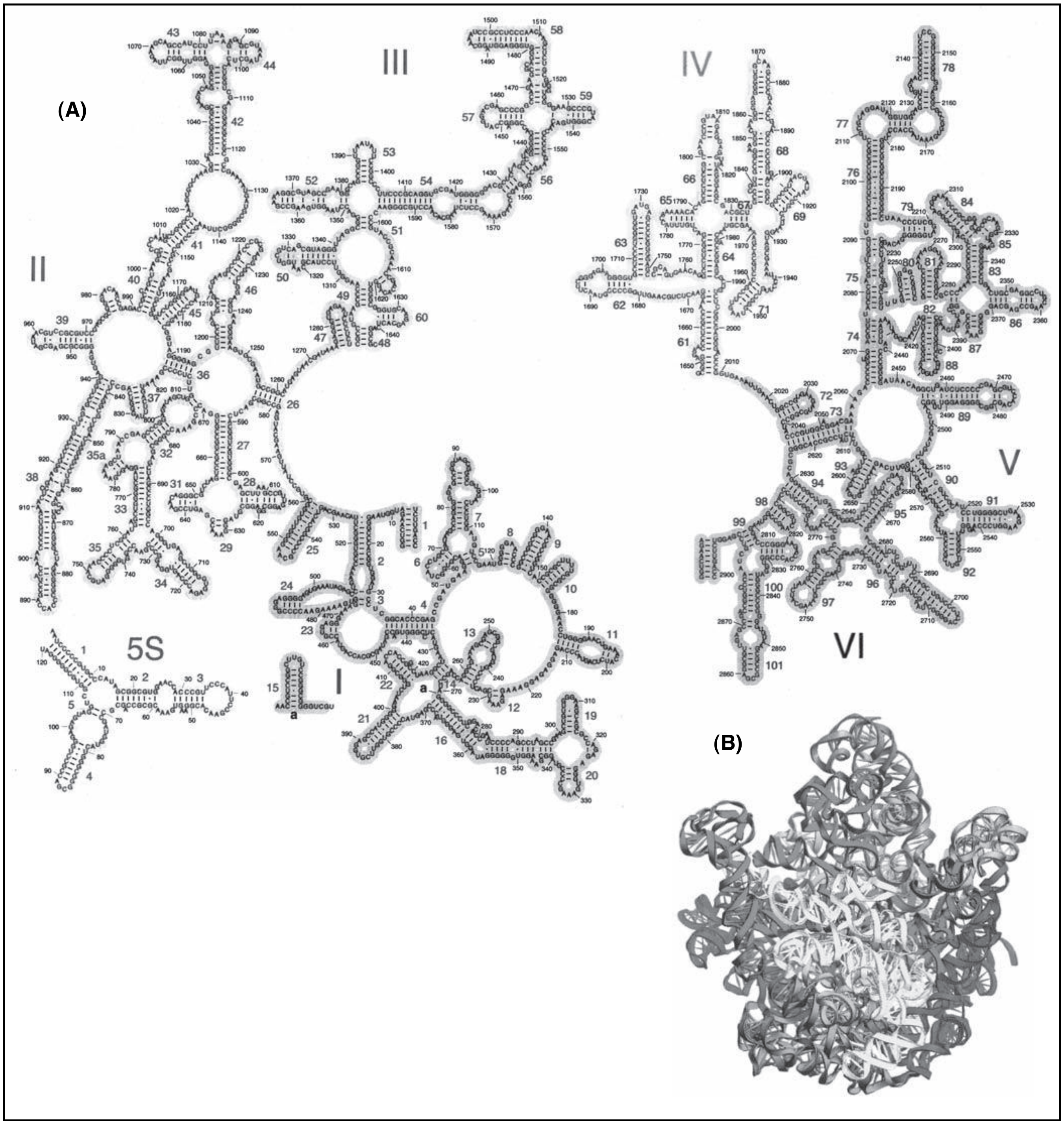


Figure 4.9. Nucleotide base layout (A) and 3-D folded structure (B) of the 23S rRNA and the 5S rRNA, comprising the large 50S subunit.[1688] (courtesy of Yusupov et al)

amino acid residue "parts" (assuming ~0.1411 kD/residue[1680]) of 20 different "parts types." Thus we may say that the bacterial ribosome assembler is a partially self-replicating machine that is built of ~10,590 "molecular parts" and 24 different "parts types." (Using the same counting method, the mammalian ribosome has ~18,780 parts.) These totals do not count the external supporting environment which includes tRNA "parts holders" and aminoacyl-tRNA synthetase "parts holder reloaders" of 20 different types each, various elongation factors that cyclically associate and dissociate with the ribosome, rRNA polymerase enzymes that construct both mRNA "instruction tapes" and rRNA feedstock molecules via transcription, various chaperone molecules to assist in proper protein folding, and the mRNA instruction tape itself. Note that because the ribosome cannot produce its own most important component, rRNA, the ribosome is not a fully self-contained self-replicating machine, but may most precisely be regarded as the key component of a self-replicating system.

During assembly operations (aka. "translation"), the space between the subunits is largely occupied by tRNAs (measuring ~6 nm wide x ~6 nm tall), whose anticodons base pair with mRNA codons in the small 30S subunit. The 3'-CCA end of each tRNA "parts holder" molecule, which carries the growing polypeptide chain and

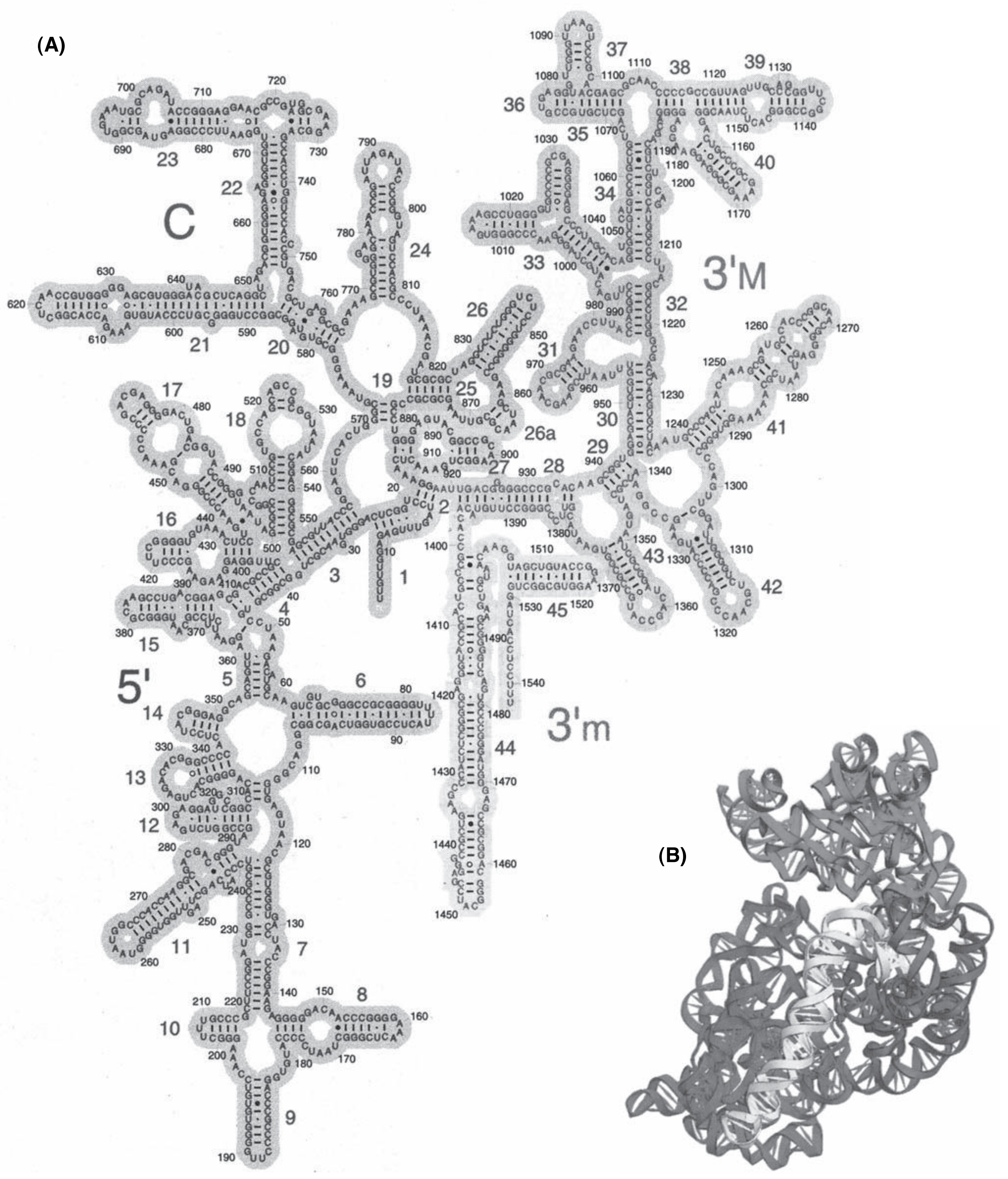


Figure 4.10. Nucleotide base layout (A) and 3-D folded structure (B) of the 16S rRNA, comprising the small 30S subunit.[1688] (courtesy of Yusupov et al)

grasps the incoming amino acid "molecular part," reaches into the large 50S subunit — the location of the peptidyl transferase center where peptide bond formation is catalyzed. In bacteria at 37 °C, 15-40 amino acids per second are added to the growing polypeptide chain[1693-1695] with an overall error rate of ~0.05% per codon that is largely due to mistaken tRNA recognition.[1693] If the bacterial ribosome's ~4.2×10^{-21} kg mass consisted entirely of proteins, then this simple biological assembler could (very loosely) be said to have a self-replication time of order 270-710 sec — the time required to synthesize its own mass, in proteins. In eukaryotes the rate of protein synthesis is often lower, sometimes as slow as ~2 residues/sec.[1693]

How does the ribosome molecular assembler work? Many details are now known,[1683-1686] but we have space here to offer only the most cursory summary. The ribosome has within its physical structure three active stations — the A site, the P site, and the E site — through which all tRNAs must pass, in sequence (A → P → E), during translation:[1693]

The **A site** (or entry site), is the only site that can be entered by an incoming tRNA with an amino acid attached to it, called an aminoacyl-tRNA. The particular desired tRNA (of 20 possible types, one for each amino acid type) must be discriminated from all its tRNA brethren along with whatever other solutes can fit into the A-site pocket using codons with only three base pairs for discrimination. (In fact, most codons use only two of the three base pairs for recognition, so some tRNAs are recognized by as few as 4 hydrogen bonds).[1697] At the start of translation, the ribosome positions itself over the mRNA tape so as to expose to the A site the codon on the tape that represents the next amino acid due to be added to the chain.

The **P site** (or donor site) lies over the mRNA codon representing the most recent amino acid to have been added to the growing polypeptide chain. This site is occupied by a tRNA to which the growing polypeptide chain is attached, called a peptidyl-tRNA.

The **E site** (or exit site) holds a tRNA from which all peptide and amino acid has been removed, called a deacylated tRNA. While the E site is occupied, the affinity of the A site for aminoacyl-tRNA is greatly reduced, preventing the next aminoacyl-tRNA from entering before the ribosome is ready. This site is transiently occupied by the tRNA en route between leaving the P site and being released from the ribosome back into the cytosol. Once released, an appropriate aminoacyl-tRNA synthetase enzyme attaches to the deacylated tRNA,[1698] adds the appropriate amino acid, then detaches, leaving behind a refreshed aminoacyl-tRNA that is ready to cycle again.

Figure 4.11 shows schematically the addition of a sixth amino acid (aa6) to a growing peptide chain that is already 5 residues long. During the next translation cycle the new aminoacyl-tRNA bearing the amino acid "aa6" enters the A site and is secured. Next, the existing polypeptide is transferred from the peptidyl-tRNA in the P site to the aminoacyl-tRNA in the A site, forging a new peptide bond (via peptidyl transferase activity on 23S[1681]) between aa5 and aa6. The deacylated tRNA moves from the P site to the E site; the ribosome translocates one codon to the right (~1.3 nm[1699]) along the mRNA tape, moving the new peptidyl-tRNA from the A site to the P site; the deacylated tRNA is ejected from the E site; and the A site is now empty and ready to accept the next aminoacyl-tRNA. Observe that all peptide "parts" and their tRNA "parts holders" (analogous to fixture-based replication; Section 5.1.8) are geometrically confined to specific locations during all key steps in translation, and chemical reactions that form covalent bonds are restricted to a specific site and are digitally sequenced. The ribosome — in effect a digitally-controlled mechanical ratchet[1686] in which peptide bond formation is driven by the codon-anticodon interaction — exhibits true positional assembly of molecular parts. There is even a special mechanism (tmRNA[1700]) to unjam and restart ribosomes that have become stalled on broken mRNA tapes.

Interestingly, the ribosome itself is assembled via self-assembly in a series of sequential reactions in which groups of proteins (built by ribosomes) associate with rRNA (made by RNA polymerases I and III,[1701-1703] themselves 500-600 kD protein-based enzymes[1680] built by ribosomes), and the structure then folds so that the next group of proteins can join.[1704-1706] Hence the ribosome requires *both* self-assembly *and* positional assembly in order to achieve its own self-replication. (In a different context, "mechanically assembled monolayers" or MAMs have been fabricated by combining the self-assembly of surface grafting molecules with mechanical manipulation of the grafting points in the underlying elastic surface).[1707]

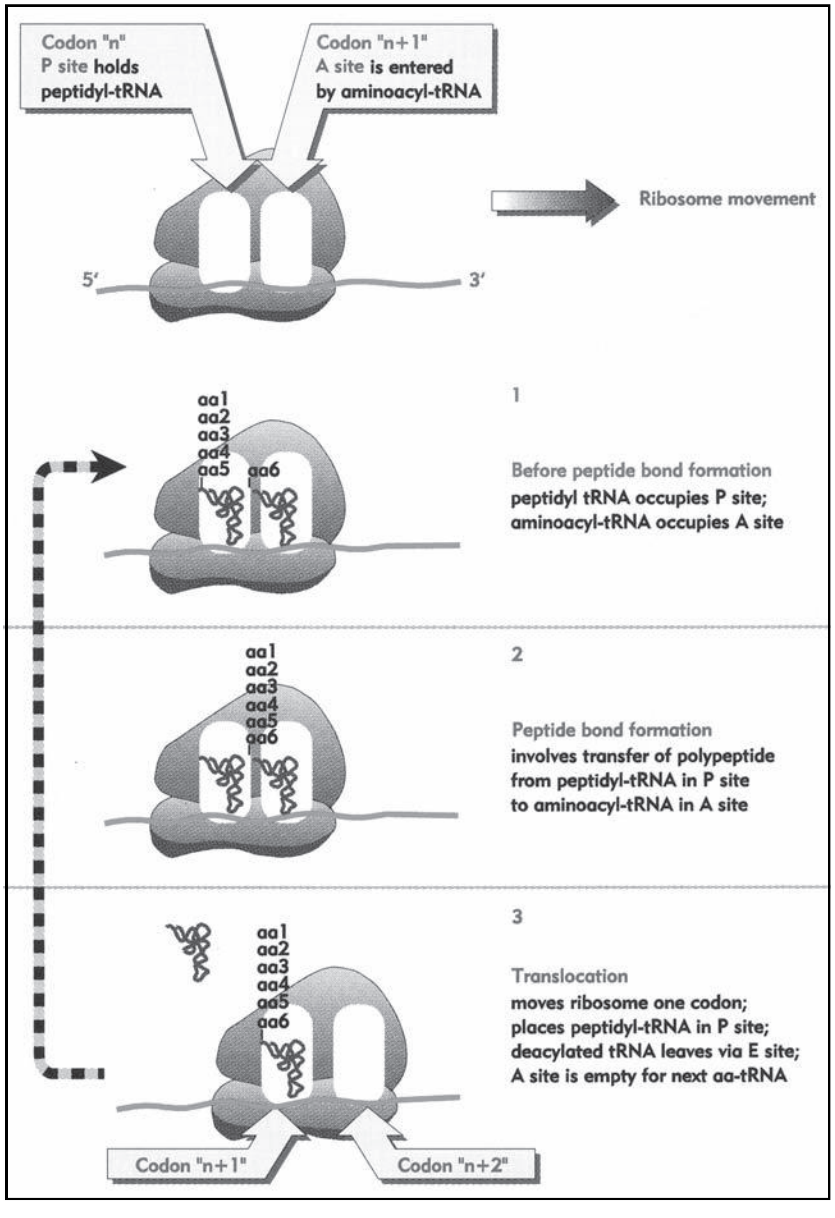

Codon "n"
P site holds
peptidyl-tRNA
Codon "n+1"
A site is entered
by aminoacyl-tRNA
Ribosome movement
5′
3′
aa1
aa2
aa3
aa4
aa5
aa6
1
Before peptide bond formation
peptidyl tRNA occupies P site;
aminoacyl-tRNA occupies A site
2
Peptide bond formation
involves transfer of polypeptide
from peptidyl-tRNA in P site
to aminoacyl-tRNA in A site
3
Translocation
moves ribosome one codon;
places peptidyl-tRNA in P site;
deacylated tRNA leaves via E site;
A site is empty for next aa-tRNA
Codon "n+1"
Codon "n+2"

Figure 4.11. Cycle of positional assembly for the ribosome. (from Genes V by Benjamin Lewin (1994), by permission of Oxford University Press www.oup.com[1693])

Other bioassembler units such as polyketide synthases and nonribosomal peptide synthetases[1708-1710] also exist and are being engineered,[1711-1715] but these enzymes generally only make one type of product per assembly. Loosely speaking, some bacteria produce polyketides in a Detroit-like assembly-line fashion.[1718-1722] These microbes contain dozens of modular enzymes, each of which assembles one component of the polyketide and then passes it along to the next enzyme in the sequence, eventually resulting in the complete synthesis. These modular synthase chains can be engineered.[1715-1717]

4.3 Natural Biological Replicators

Biology has given rise to many different forms of self-replication, from simple to complex. The logical similarities between living organisms and von Neumann's kinematic automaton have been noted by Sugita[314] and others, and there is clearly also the possibility of engineering artificial versions of these natural systems, especially artificial cellular replicators (Section 4.4). Investigations of artificial molecular replicators might also lead to new insights into the origin of life on Earth.[1723,1724] For example, Dyson[2397] has suggested that Earth life might have originated by a symbiotic combination of two very different kinds of replicators — non-Mendelian replicating oil droplets enclosing homeostatic metabolic chemical systems that absorbed raw materials from their surroundings, and initially-parasitic molecules of DNA that infected the droplets and took advantage of the existing metabolic machinery in order to reproduce. Compartmentalization is generally regarded as useful for replicative machinery.[1725] Woese[1726] notes that key steps in the origin of life — called crossing the "Darwinian Threshold" — include the incorporation of information storage and feedback mechanisms in supramolecular prebiotic assemblies.

Natural biological replicators include pure protein forms (prions), pure nucleotide forms (viroids), protein-encased nucleotide forms (viruses), and more complex cellular forms (prokaryotes and eukaryotes). Besides simple unit replicators, biology also exemplifies factory-like modes of replication in which two or more separate entities cooperate symbiotically to achieve replication of the whole. In some cases, such as the mitochondrion (Section 4.3.7), the symbiosis has become obligate for all parties — the mitochondrion alone cannot replicate itself (via growth and fission) outside of the cell because it requires the assistance of cell-supplied proteins and lipids, and the cell alone cannot replicate itself because it needs the mitochondria to produce ATP, the principle intracellular energy molecule. Even in viruses where the relationship with infected hosts is usually obligate only for one party (the virus) and is usually considered parasitic, examples of mutually obligate virion-eukaryote symbiotes are known.[1727] In other cases, the symbiosis may be merely facultative. For example, lichens[1728-1731] are two- or three-way symbionts of fungi (the mycobiont), algae (the photobiont), and sometimes also cyanobacteria (a photobiont and nitrogen source) combined into a single body (the thallus). Each of the three components is an independently viable replicator, but by combining together the system can inhabit a wider variety of environments. The several hundred *Chlorella* algae which are dispersed throughout the cytoplasm of *Paramecium bursaria* are another example of facultative symbiosis among independent cellular replicators.[1732]

4.3.1 Prions

Prions have been described by Prusiner[1733] as "the only known example of infectious pathogens that are devoid of nucleic acid. All other infectious agents have genomes composed of either RNA or DNA that direct the synthesis of their progeny." In mammals, prions (Figure 4.12) replicate by recruiting normal cellular prion protein and stimulating its conversion to the disease-causing prion isoform (e.g., "scrapie prion").[1733] Modified (pathogenic) prion protein acts as a template upon which normal prion protein is refolded into a nascent modified protein through a process facilitated by another protein.[1734]

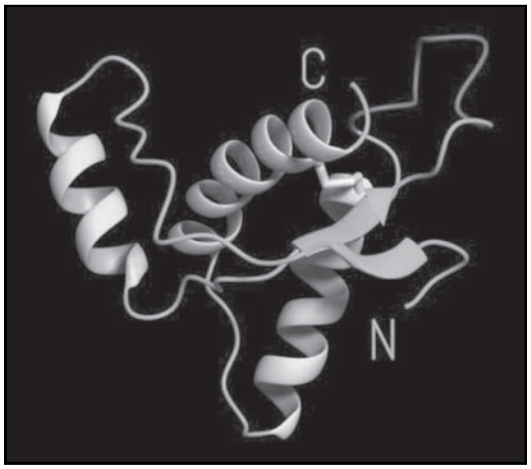


Figure 4.12. Schematic image of mouse prion domain PrP(121-321); image originally prepared and courtesy of Martin Billeter and Roland Riek.[1735]

The normal cellular prion protein is converted into modified protein through a post-translational process during which it acquires a high beta-sheet content.[1734] In particular, the polypeptide chains of normal prion and scrapie prion are identical in composition but differ in their 3-dimensional folded structures: normal prion is rich in alpha helices (spiral-like formations of amino acids) with few beta sheets (flattened strands of amino acids), whereas scrapie prion is poorer in alpha-helices and has many more beta-sheet domains.[1733] This structural transition from alpha-helices to beta-sheet in prion protein is apparently the fundamental event underlying prion disease.* [1733] Since scrapie prions can induce ordinary prion protein to refold into more scrapie protein, they represent an example of a self-replicating molecule[1368,1736-1738] that employs a self-replicating geometry roughly analogous to the Penrose blocks (Section 3.3). The fastest-reported prion refolding event measured to date[1739] is for *m*PrP(121-231), the ~15.7 kD structured 111-residue domain of the murine cellular prion protein PrP^C (a strongly conserved cell surface glycoprotein totaling 231 amino acids in size), and occurs without kinetic intermediates at an extrapolated rate at 4 °C of 4000 sec^{-1} (~170 microsec half-life).

Prions are responsible for the transmissible spongiform encephalopathies (TSEs) including mad cow disease, scrapie, and the human Creutzfeldt-Jakob disease.

4.3.2 Viroids

Subviral plant pathogens first discovered in 1971,[1741] viroids and viroid-like RNAs[1742] are small, single-stranded, closed-circuit RNA molecules existing as highly base-paired rod-like structures (Figure 4.13) without protein coats (i.e., without capsids). Viroids typically contain 246-401 nucleotides,[1743] have mass ~100 kD, have a compact secondary structure, lack mRNA activity,[1744] and replicate autonomously (Figure 4.14) when inoculated into their host plants.[1743]

---

* *The abnormal isoform also differs physically from the normal cellular isoform by its insolubility in detergents, its propensity to aggregate, and its relative resistance to breakdown by hydrolysis.[1740] Limited proteolysis of scrapie prion produces a smaller and protease-resistant molecule of approximately 142 amino acids which polymerizes into amyloid.[1733] Prions also appear to encode strain-specific properties in the tertiary structure of the modified prion protein.[1734]*

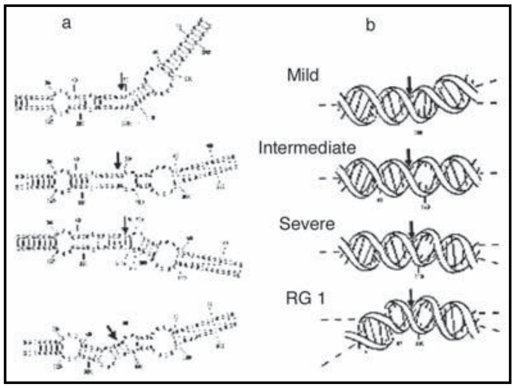


Figure 4.13. Viroid structure.[1745] (a) Schematic representations of the thermodynamically optimal secondary structures of the pathogenicity domain (nucleotides 36-67 and 292-325) of several infectious potato spindle tuber viroid variants; (b) Two-dimensional representations of their respective three-dimensional structure, assuming a standard A-type RNA helix with the helix axis bent to compensate for missing nucleotides in asymmetrical loops; helix axes shown by dashed lines.[1745] (courtesy of R.A. Owens)

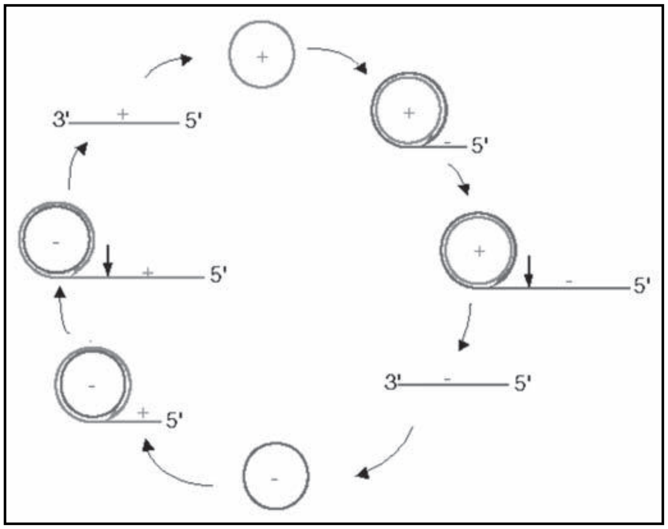


Figure 4.14. Schematic of the symmetric pathway of viroid replication, courtesy of Demin Zhou.[1746] Starting with the positive viroid (top circle), a complimentary multimeric copy is first created with RNA polymerase via rolling circle replication. Next, the negative multimer self-cleaves by hammerhead ribozymes into a single linear monomer followed by (possibly autocatalytic) ligation. The process then repeats itself for the complementary strand, completing the cycle and regenerating the viroid.[1746] Some viroids follow an alternative asymmetric pathway in which cleavage of multimers is not autocatalytic.

Viroids replicate themselves only in an intracellular environment. Notes Flores[1743] in a recent review: "In contrast to viruses, viroids do not code for any protein and depend on host enzymes [e.g., a specific RNA-dependent RNA polymerase] for their replication, which in some viroids occurs in the nucleus [usually in nucleoli] and in others [occurs] in the chloroplast, through a rolling-circle mechanism with three catalytic steps. Quite remarkably, however, one of the steps, cleavage of the oligomeric head-to-tail replicative intermediates to unit-length strands, is mediated in certain viroids by hammerhead ribozymes that can be formed by their strands of both polarities. Viroids induce disease by direct interaction with host factors, the nature of which is presently unknown. Some properties of viroids, particularly the presence of ribozymes, suggest that they might have appeared very early in evolution and could represent 'living fossils' of the precellular RNA world that presumably preceded our current world based on DNA and proteins." Along with human hepatitis delta virus (vHDV), viroids are the smallest known natural auto-replicable RNAs[1742] or "autonomous replicons".[1747,1748] (Spiegelman's mutant molecule (Section 5.5) is a slightly smaller RNA strand but requires a very specialized unnatural environment in which to replicate.)

Viroid replication rate following the symmetric pathway can be crudely estimated by applying the 50-100 nucleotide/sec rate constant typical of bacterial RNA polymerases to the 246-401 viroid bases, then adding two hammerhead- or RNAase-mediated cleavages of intermediates which occur at a 1.5 min^{-1} rate (~40 sec per cleavage),[1749] gives an estimated ideal viroid replication time of ~ 80-90 sec.

Computer simulations of viroid folding pathways[1750] are the first step towards the rational design of artificial viroids.

4.3.3 Viruses

Viruses are acellular bioactive parasites that attack virtually every form of cellular life[228] and which cannot replicate except in the presence of a biological host cell. Viruses have diameters ranging from 16-300 nm[1751] — for example, poliomyelitis ~18 nm, yellow fever ~25 nm, influenza ~100 nm, herpes simplex and rabies ~125 nm, and psittacosis ~275 nm.[1752] Their shape is either pseudospherical with icosahedral symmetry, as in the poliomyelitis virus, or rodlike, as in the tobacco mosaic virus (TMV). Viruses consist of a core of RNA (most plant viruses and animal viruses such as the rhinoviruses, polio and flu viruses, and all retroviruses) or DNA (most bacterial and some animal viruses), but never both. This nuclear material is surrounded by a protein coat called a capsid, a quasi-symmetrical structure assembled from one or only a few protein subunits called capsomeres. A virus surrounded only by capsid is a naked virus; some viruses acquire a lipid membrane envelope from their host cell upon release, and are then called enveloped viruses. Attached to the capsid are other protein structures necessary for host infection, especially attachment or docking proteins and most importantly the ATP-powered DNA packaging motor (Section 4.5) that stuffs viral genetic material into the viral capsid.[1753-1755] The interior capsid volume is usually only slightly larger, and never more than twice as large, as the volume of the enclosed nuclear material.[1693] For instance, the adenovirus (one family of viruses that causes the common cold in humans) is an icosahedral particle ~70 nm in diameter (~180,000 nm^3) containing one double-stranded DNA molecule ~11 microns (~35,000 bases or ~10^7 daltons) in length (~15,000 nm^3), giving a composition of approximately 92% protein and 8% DNA by volume. By comparison, the TMV has 5% nucleic acid, the bushy stunt virus 17%, and the tobacco ringspot virus has 40%.[1752]

Bacteriophage viruses, first employed therapeutically against bacteria by d'Herelle in 1922,[1756] have recently been used as self-replicating pharmaceutical agents.[1757] One of the best-studied examples of the bacteriophages is the T4 virus (Figure 4.15). Like all viruses, T4 replicates primarily by self-assembly[1758-1762] in the final stage, albeit with the assistance of co-opted host-cell ribosomes (Section 4.2) — which are positional-assembly style devices — to make the "parts". (Self-assembly and positional assembly are distinguished in the introduction to Chapter 4). The syringelike, 100-nm long, 20-nm wide cylindrical T4 tail assembly, made of 15 different proteins joined in 24 annular segments

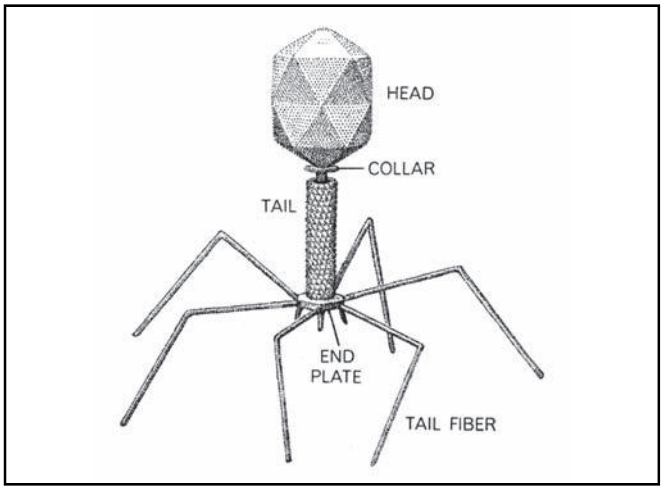


Figure 4.15. T4 bacteriophage virus.[1769] Copyright 1965 Scientific American; online image courtesy Nanomedicine Art Gallery, Image 101; http://www.foresight.org/Nanomedicine/Gallery/Captions/Image101.html.

with an 8-nm inside bore, has a set of small fibers near the tip that attach to the plasma membrane of the host cell. After a lysozyme-like enzyme opens a breach in the host cell wall, the tail sheath thickens and contracts,[1763] inserting a ~2.8 megadalton hollow core protein nanotube (80 nm long, 7 nm wide, 2.5 nm inside bore) through the host cell integument. The protein nanotube is then uncorked in response to chemical signals, and large-molecule (mostly putrescine and spermadine) pressurization of ~30 atm ejects a single 70-micron long, 2-nm wide DNA thread (~50% of T4 head volume) through the 2.5-nm nanotube aperture and out into the cell typically in ~3 seconds, a mean flow velocity of ~23 microns/sec.[1764] (Phage DNA is mechanically packed into capsids by molecular motors).* [1753] The double-stranded DNA thread rotates ~4000 times around its axis as it emerges.[1765] Under optimum conditions, initial injection velocity may start as high as 360 micron/sec with a minimum injection time of 0.23 sec.[1764] Once inside the host cell, the virus (specifically, its genetic material) uses the cell's machinery, including some of the cell's enzymes, to generate virus parts and the 168 kilobase T4 genome,[1766] which self-assemble into new T4 virus particles (Figure 4.16). The phage head, tail, and tail fibers are assembled via independent pathways, and then are joined to form the complete virus.[1767] A single *Escherichia coli* bacterium injected with a single T4 phage virion at 37 °C in rich media lyses after 25-30 minutes (the first completed virus particle, est. mass ~0.3 fg, materializes ~13 minutes post-infection[1758]), releasing 100-200 phage particles that have replicated themselves inside the cell.** [1768]

Thus the general logic of viral replication (Figure 4.17) appears to be to impose the exogenous viral "data tape" upon the cellular manufacturing machinery. This captive machinery fabricates all viral parts more or less simultaneously, whereupon these parts then self-organize by making use of prearranged conformational switching (Section 4.1.5) of the physical structure of parts and subassemblies as they self-assemble into new complete virion particles.

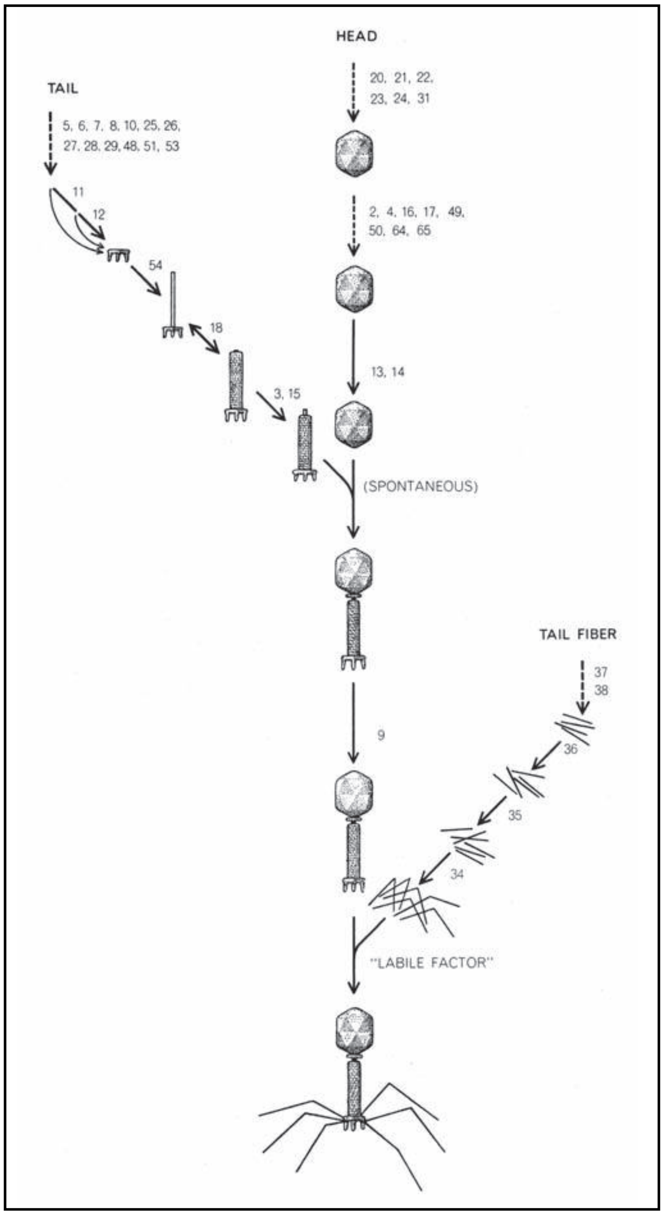


Figure 4.16. Self-assembly of bacteriophage T4 in ordered sequence from its individual component parts.[1769] (Copyright 1965 Scientific American)

4.3.4 Prokaryotic Cells

Bacteria are unicellular microorganisms capable of independent metabolism, growth, and replication,[1771] but lacking a distinct nucleus (prokaryotes). Their shapes are generally spherical or ovoid (cocci), cylindrical or rodlike (bacilli), and curved-rod, spiral or comma-like (spirilla). Bacilli may remain associated after cell division and form colonies configured like strings of sausages. Bacteria range in size from 0.2-2 microns in width or diameter, and up to 1-10 microns in length for the nonspherical species. The largest known bacterium is *Thiomargarita namibiensis*, with spheroidal diameters from 100-750 microns.[1772] Spherical bacteria as small as

---

** Here we are describing only one well-known process of bacterial-assisted replication of an extensively studied bacterial virus. R. Bradbury notes that there are human viruses such as CMV and HSV that contain more than an order of magnitude more DNA and have a correspondingly more complex life cycle and assembly process.*

*** This describes only the* lytic cycle *of viral reproduction. In the alternative* lysogenic cycle *of some bacteriophage viruses, the phage's DNA inserts itself into the bacterial chromosome, becoming a "prophage." A host cell that carries a prophage has the potential to lyse, thus is called a lysogenic cell.*

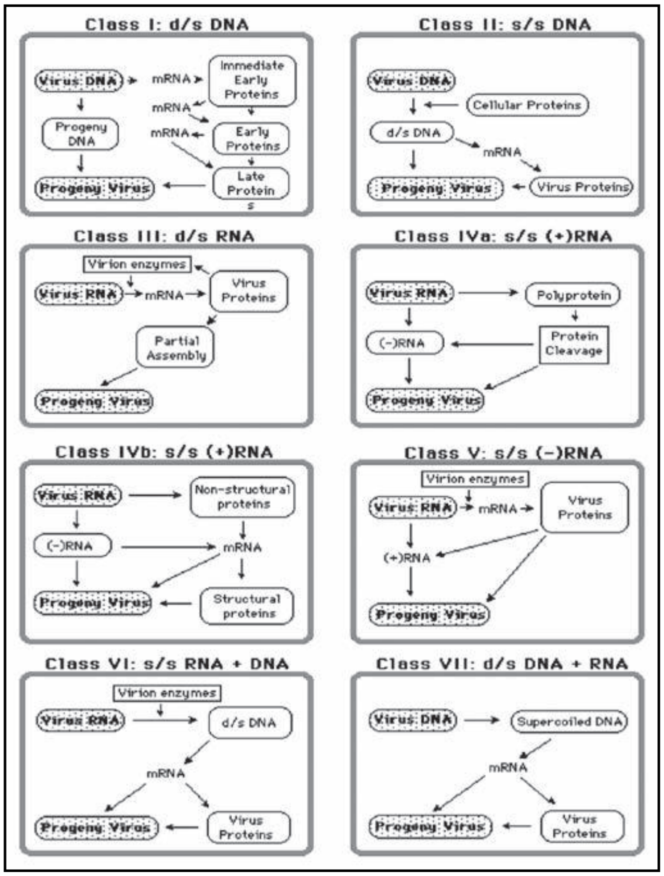


Figure 4.17. Virus replication strategies, courtesy of Alan J. Cann.[1770] Viruses use different replication strategies for different genome types, of which there are eight (arbitrary) groups: **I:** Double-stranded DNA (Adenoviruses; Herpesviruses; Poxviruses, etc); **II:** Single-stranded (+)sense DNA (Parvoviruses); **III:** Double-stranded RNA (Reoviruses; Birnaviruses); **IV(a/b):** Single-stranded (+)sense RNA (Picornaviruses; Togaviruses, etc); **V:** Single-stranded (-)sense RNA (Orthomyxoviruses, Rhabdoviruses, etc); **VI:** Single-stranded (+)sense RNA with DNA intermediate in life-cycle (Retroviruses); and **VII:** Double-stranded DNA with RNA intermediate (Hepadnaviruses).

50-500 nm in diameter have been reported.[1773] It has been theorized that the smallest possible cell size into which the minimum essential molecular machinery can be contained within a membrane is a diameter on the order of ~40-50 nm,[1774] though the current consensus among biologists is that a somewhat larger minimum size may be required (Section 5.3). Many spherical bacteria are ~1 micron in diameter; an average rod or short spiral cell is ~1 micron wide and 3-5 microns long. Each bacterial cell consists of a mass of protoplasm enclosed within the usual thin lipid bilayer plasma membrane. Most Gram-positive bacteria are surrounded by a thick, mechanically strong but porous peptidoglycan cell wall. Gram-negative bacteria like *E. coli* surround themselves with an additional two-layer coat atop the peptidoglycan layer.

Bacterial cells possess small internal vacuoles, ribosomes, granules of stored food, and usually one or more externally-attached flagella, but have no internal membranous surfaces, no internal organelles (although some functional compartmentalization does exist[1775]), and no distinct nucleus. A single circular chromosome is organized into one or more compact aggregates, called nucleoids, that may occupy about one-third of cell volume.[1693] *E. coli*, a well-studied cylindrical bacterium typically measuring 0.65 microns wide and 1.7 microns long (cell volume ~ 0.6 micron^3), has one double-stranded DNA chromosome that measures ~1.3 mm (~4.2 megabases or ~10^9 daltons) in length (strand volume ~ 0.002 micron^3), organized in ~40 kilobase loops,[1693] during resting phase.

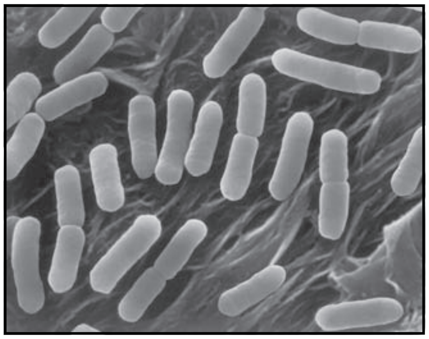


Figure 4.18. Rod-shaped *E. coli* bacteria undergoing cell division. (hemorrhagic *E. coli*, strain 0157:H7 (division) (SEM 22,810X); image copyright Dennis Kunkel Microscopy, Inc. at www.DennisKunkel.com, used with permission.)

During binary fission (Figure 4.18), the normal method of bacterial self-replication, the bacterium starts with its genetic material, a circular chromosome of DNA, attached at one spot on the inner cell membrane, but otherwise fairly loose inside the cell. Chromosomal replication[1776] begins at a specific sequence of nucleotides called the origin. Enzymes called helicases recognize this specific sequence, bind to this site, and begin unwinding the DNA by breaking the hydrogen bonds that hold the double strand together, creating a "replication fork." Single-stranded binding proteins attach in chains along the separated strands for stabilization and to prevent rewinding. After the enzyme primase creates a short priming sequence, highly reactive free nucleoside triphosphates in the cytoplasm begin pairing up with their complementary bases on the exposed parental strand. Once properly aligned, the triphosphates are joined to the growing strand by an enzyme called DNA polymerase which catalyzes the hydrolysis of the phosphates as the nucleotide is added to the strand, forming a phosphodiester bond.

The polymerase continues around an entire strand until the duplicate copy is complete. The two duplicate chromosomes are attached at different ends of the cell membrane, called "pole preference".[1777] The cell continues to take in food, metabolizing nutrients, building proteins via ribosomal translation of mRNA transcripts, increasing its mass and elongating, causing the two points of chromosome attachment on the cell membrane to grow apart. Once the bacterium has reached twice its initial size, its plasma membrane thickens and forms a division septum,[1778] pinching inward at the center of the cell, the full invagination finally causing the cell to divide, with a new cell wall separating two now-independent "daughter cells" having duplicate chromosomes. When each daughter again reaches a threshold "parental" size, the replication cycle can begin anew. Under optimal growth conditions the cycle may take only 15-20 minutes in *E. coli*.[1771] Note that the logic of replication in bacteria is, first, to duplicate the information tape, and then, second, to manufacture the construction engine, the same as the classical von Neumann kinematic replication scheme (Section 2.1.1).

In modern biotechnology, bacteria are often employed as "self-replicating factories"[1779-1781] for various useful products.

4.3.5 *Plasmids*

Plasmids[1782,1783,1793] are extrachromosomal elements found in most bacteria (and also in some eukaryotic cells). A plasmid is an autonomous circular DNA genome that may replicate along with the bacterial genome (Figure 4.19) or may be under a different type

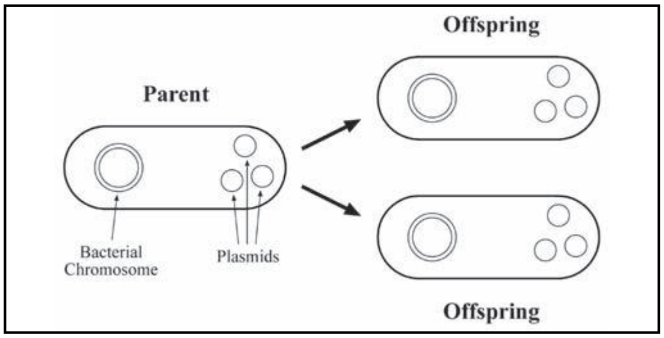


Figure 4.19. Schematic of plasmid replication.

of control.[1693] Usually the genetic information found in the plasmid is dispensable, contains no housekeeping genes, and thus is not required in bacterial everyday life.[1782] Some plasmids are cryptic, apparently containing nothing of particular value for the cell, and may be considered purely "selfish DNA" — both in prokaryotic[1784] and eukaryotic[1785] host cells. Other plasmids confer selective advantage[1786] to the host cells under certain conditions, including, for instance, genes associated with virulence, antibiotics resistance,[1787] metal uptake or resistance, or intercellular transfer.

Plasmids must be replicated, their genes transcribed and their mRNAs translated, imposing a parasitic energetic cost (and presumably a competitive disadvantage) on the host cell which should be selected out over time.[1782] However, the clever plasmid usually has developed means of being maintained stably in a host cell population,[1788,1795] using stability functions[1782] of: (1) the partition type, wherein a centromere-like apparatus is used to partition plasmid copies so that each bacterial daughter cell (at cell division) acquires at least one copy; (2) the killer type, wherein plasmids encode conditional killer proteins which only are produced when a cell has lost a plasmid (sort of a memory function used to punish a naughty host cell); or (3) the site-specific recombination type, wherein enzymes make two plasmids from one copy (which is a dimer), helping stability by keeping the number of plasmid molecules high enough for proper segregation.

In addition, all known real plasmids carry a basic replicon, a set of genes and sites needed for controlling copy number.[1789-1793] Wagner[1782] observes that plasmids have defined copy numbers (number of molecules per cell) in given bacterial cells under given sets of physiological conditions. If plasmids were unable to make head counts and correspondingly regulate their own replication (which is always carried out using host enzymes), their copy numbers would fluctuate because of natural physiological variations. After many generations of growth, this would result in bacterial populations in which some cells might contain as little as one plasmid at cell division while others could carry hundreds. Such a scenario is not beneficial for a plasmid, since in the first case, one of the daughter cells will have lost the plasmid, in the second case the plasmid load may kill the host cell. Hence, plasmids have evolved copy number control systems. Copy number control is homeostatic: a plasmid can "measure" its copy number in the cell, and use this information to affect the replication frequency at the plasmid origin of replication. Plasmids use different devices to accomplish this, including iterons (repeated DNA sequences)[1793,1796] and antisense RNAs.[1793-1795]

4.3.6 Eukaryotic Cells

The replication of eukaryotic plant and animal cells (cells having a distinct nucleus and organelles) is a somewhat more complex process than for prokaryotes (cells having no distinct nucleus or membrane-enclosed organelles), following a tightly controlled cell cycle program[1797-1802] with well-defined phases (Figure 4.20). There are even checkpoints[1803] to verify that each phase has been successfully completed, and if not, the cell may be compelled to self-destruct (e.g., undergo apoptosis[1804]). Eukaryotes span a considerable size range. For example, most human cells measure between 2-120 microns in diameter.[228]

Cells not currently replicating are said to be in the G0 phase, and begin the replicative process by entering the cell cycle at the first "gap" or G1 phase. G1 phase typically lasts 6-12 hours and is the first growth phase, during which time the cell increases its mass and both RNAs and proteins are synthesized, but there is no DNA replication. Following G1 (and after passing a commitment checkpoint) is the "synthetic" S phase, lasting 6-8 hours, wherein new DNA is synthesized and the existing chromosome set is duplicated.[1805] (Note that a few plant eukaryote reproductive cycles include complete organisms that are haploid, not diploid).[1806] The cell also continues to grow during S phase. All this activity depletes the cell's energy resources, so a second period of growth (without DNA synthesis) follows, called the second "gap" or G2 phase, lasting 3-4 hours. Finally having rebuilt its physical resources (and after passing another commitment checkpoint), the cell now enters M phase or mitosis, lasting <1 hour, whereupon the nuclear material is separated and the parent cell divides into two daughter cells. Virtually all biochemical synthesis activities come to a halt during M phase.[1807] The daughter cells are born into G1 phase, and may either proceed through another replicative cell cycle or may exit the cycle and enter the noncycling G0 phase.

Mitosis[1808-1810] itself is a highly structured process involving several distinct phases (Figure 4.21) and checkpoints[1811,1812] of its own, including:

Interphase — all parts of the cell cycle excluding mitosis; cell metabolism is normal and DNA is replicated in preparation for mitosis to begin; the single centrosome replicates[1813-1817] to form two centrosomes, both located outside the nucleus (animal cell centrosomes contain structures called centrioles).

Prophase — nucleoli disappear from the nucleus; chromatin fibers (DNA) condense, coil tightly, and become visible as chromosomes with both sister chromatids joined at the centromere; the mitotic spindle (made of microtubules and associated proteins) begins to form; centrosomes move away from each other, propelled by the lengthening of microtubular bundles.

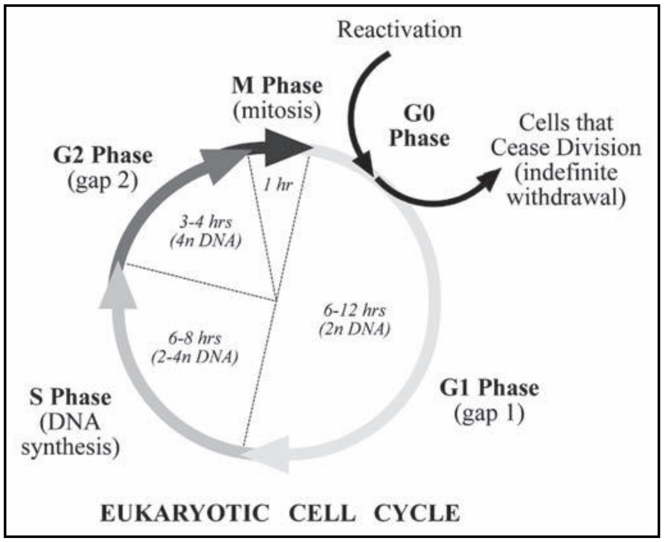


Figure 4.20. The eukaryotic cell cycle. (revised from Lewin[1693])

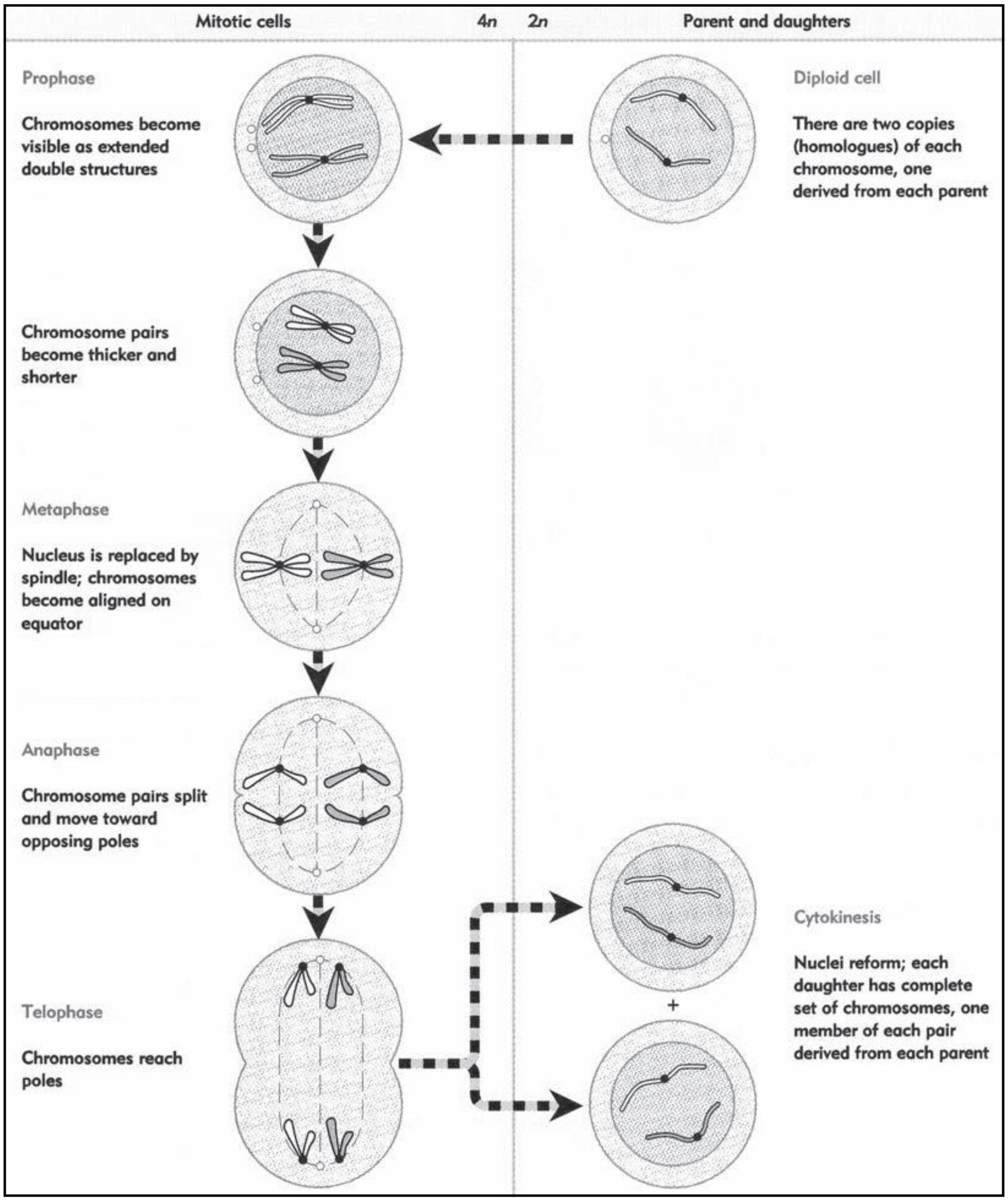

Mitotic cells
4n
2n
Parent and daughters
Prophase
Chromosomes become visible as extended double structures
Diploid cell
There are two copies (homologues) of each chromosome, one derived from each parent
Chromosome pairs become thicker and shorter
Metaphase
Nucleus is replaced by spindle; chromosomes become aligned on equator
Anaphase
Chromosome pairs split and move toward opposing poles
Telophase
Chromosomes reach poles
Cytokinesis
Nuclei reform; each daughter has complete set of chromosomes, one member of each pair derived from each parent
+

Figure 4.21. Schematic representation of the phases of eukaryotic mitosis. (from Genes V by Benjamin Lewin (1994), by permission of Oxford University Press www.oup.com[1693])

Prometaphase — the nuclear membrane separates into fragments and then is disassembled; microtubules invade nuclear region and interact with condensed chromosomes; spindle fibers extend from each pole and move toward the equator; some microtubules connect to the kinetochore (a specialized attachment region on each chromatid which lies in the constricted region defined by the centromere) while other microtubules radiate to the equator.

Metaphase — with the centrosomes at opposite ends of the cell, the chromosomes convene on the equatorial metaphase plate (the middle region); chromosome centromeres are aligned and the identical chromatids are attached to kinetochore tubules radiating from each pole.

Anaphase — paired centromeres of each chromosome divide, liberating sister chromatids from each other; spindle fibers shorten, pulling the newly synthesized chromosomes (DNA) to one end of the cell and the original chromosomes to the other end of the cell; the cell begins to pull apart.

Telophase — non-kinetochore fibers continue to elongate the cell; chromosomes begin to uncoil; daughter nuclei begin to form (opposite of prometaphase). A cleavage furrow forms and the two cells split apart, a process called cytokinesis. In animal-cell cytokinesis, a cleavage furrow appears, beginning as shallow groove in cell surface. On the cytoplasmic side of the furrow, a contractile ring of microfilaments is made from the protein actin; as the ring of microfilaments contracts, the cleavage furrow deepens until the parent cell is pinched apart into two daughter cells. In plant cells, a cell plate forms across the equator during telophase, whereupon vesicles from the Golgi body are driven along microtubules to the middle of the cell and the subsequent fusion of vesicles forms the membranes.

As with bacteria, the replicative logic for eukaryotes seems to be: Starting with one parent replicator, build enough of the constructor to enable tape copying, then replicate the instruction tape, then finishing building the rest of the constructor, which is composed of many specialized devices like a factory (e.g., ribosomes, mitochondria, Golgi membranes, etc.). Once there are two instruction tapes and enough factory devices to comprise two complete constructors, and a sufficient reserve of stored energy, the tapes and factory devices are distributed into two systems of roughly equal size having nearly identical sets of components. The two identical systems are then physically separated, making two independent daughter replicators.

4.3.7 Mitochondria

Mitochondria are energy-producing organelles present in virtually all eukaryotic cells. After the nucleus and the endoplasmic reticulum, the mitochondrion is often the largest organelle in most animal cells and is most likely an ancient endosymbiont[1818] of the eukaryotes. (Even secondary endosymbiosis, eukaryotes engulfing eukaryotes, has been found in cryptomonads[1819-1821] and chlorarachniophytes).[1820-1822] The typical time-averaged dimensions of the mitochondrion are roughly cylindrical, with a 0.5-1.0 micron diameter and a ~3 micron length (and rarely, up to 10 microns[1823]) — about the size of a bacterium (~1 μm^3 or ~1.2 x 10^{-15} kg each). Except for plant chloroplasts, mitochondria are unique among organelles in having their own DNA genomes, ribosomes and tRNAs that are quite different from those found in the cytoplasm. The interior of the mitochondrion is filled with a semifluid gel-like matrix that contains a concentrated mixture of hundreds of different enzymes related to aerobic cellular respiration and oxidation, plus several identical copies of the mitochondrial mtDNA genome which encodes the two RNA species present in mitochondrial ribosomes (12S and 16S rRNAs), a full set of transfer RNAs (22 genes) required for protein synthesis,[1824] and 13 polypeptide constituents of respiratory chain complexes.[1825] The mitochondrial genome[1825,1826] consists of a circular DNA molecule of ~11 million daltons, coding for about a dozen polypeptides. The human mtDNA molecule has 16,569 base pairs and a contour length of ~5 microns (cf. 16,831 base pairs for elephant mitochondria,[1827] etc.).

When cellular requirements for ATP increase, mitochondria pinch in half (i.e., binary fission; Figure 4.22) to increase their numbers, then both halves regrow to the former full size.[1828] (Doubling time for mitochondria in chloramphenicol-treated *Tetrahymena pyriformis* cells is ~2 hours,[1829] and 2-5 hours in *Physarum polycephalum* cells under starvation conditions).[1830] It is a process very similar to the replication of prokaryotes, with DNA polymerase gamma processing the mtDNA, except that over evolutionary timescales many of the genes needed for independent replication have been offloaded to the much larger genome residing in the eukaryotic cell nucleus. Thus mitochondria are self-replicating organelles, but they require the assistance of cell-supplied proteins and lipids.

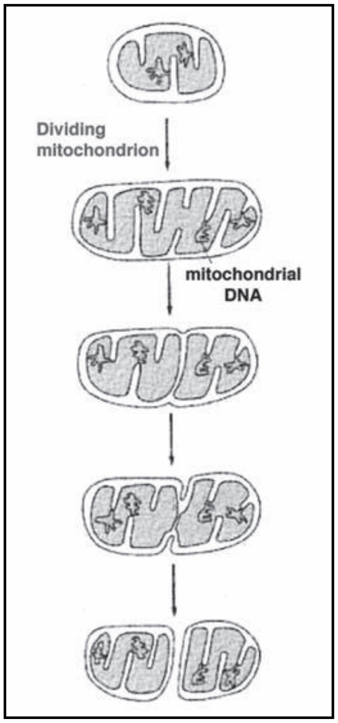


Figure 4.22. Schematic of mitochondrial replication.[1831]

This illustrates yet another interesting variant in the logic of kinematic self-replication. Just as "inherently safe" (Section 5.11) replicators may be created by employing the "broadcast architecture"[208-210] wherein key information (instructions) essential for replication is exclusively provided from without, inherently safe replicators may *also* be created by employing a "vitamin architecture" in which key materials (physical components or parts) essential for replication are exclusively provided from without. In kinematic replicator theory, such key materials or components have often been called "vitamin parts".[2,216,271]

So, for example, if any of three specific outer membrane proteins — Mmm1p,[1832] Mdm10p,[1833] and Mdm12p[1834] — are removed from a mitochondrion, then fission is not possible and the result is one giant parent mitochondrion instead of two smaller daughter mitochondria. These three proteins may be considered as "vitamin parts" relative to mitochondrial replication. Similarly, most mitochondrial lipids, the vast majority of mitochondrial proteins (including DNA and RNA polymerases, ribosomal proteins, aminoacyl tRNA synthetases, etc.),[1835,1836] and even the mitochondrial 5S rRNA[1837] are encoded by nuclear DNA and synthesized in the extramitochondrial cytosol, and thus must be imported into the mitochondrion as additional "vitamin parts" for replication to occur. (See also Sections 5.6 and 5.1.9 (A1, E4, I3).)

4.3.8 Large Metazoans

We will not attempt to document here or to describe the many varied and entertaining ways in which large multicellular lifeforms including plants[1838-1840] and animals,[1841-1846] and especially humans[1847-1849] along with their memetic[525] and cultural[1851-1857] structures, may undertake self-reproduction. However, the common replicative strategy may be crudely summarized as follows: First, manufacture fertile seed(s) or egg(s); second, establish an environment in which the seed(s) or egg(s) can grow into a much larger, mature adult forms; and third, use the large adult forms to manufacture more seed(s) or egg(s), repeating the cycle.

The advent of sex in reproduction (Section 5.1.9 (L1)), while useful in producing variation upon which evolution may work, nevertheless greatly complicates matters at the cellular level because two separate genomes must now be replicated, recombined, partially purged, then rejoined while keeping the final chromosome count constant. For example, in human females the primary oocytes in the ovaries remain in suspended development until the monthly onset of ovulation. At that time, during each cycle a single primary oocyte grows larger and completes meiosis I (separation of homologs): the chromosomes (two sets of 23 pairs, or 92 chromosome strands, after chromosome duplication) are recombined (genetic material is swapped between strands) with their pair members. After that, half of the chromosomes (46 strands) are expelled in a "polar body," restoring the number of copies to two (46 chromosome strands) in the remaining secondary oocyte. The polar body is essentially a waste receptacle that receives little more than the surplus chromosomes. In humans and most vertebrates, the first polar body does not go on to meiosis II (separation of sister chromatids). Which chromosomes end up in the egg and which end up in the disposable polar body is entirely a matter of chance. After entry of a sperm cell during fertilization, the secondary oocyte completes a second meiotic division (meiosis II), yielding a fertilized egg (each of which contains only a single set of 23 maternal chromosome strands, along with the 23 paternal strands contributed by the sperm) and throwing off a second polar body (carrying off a surplus set of 23 maternal chromosome strands). Avoiding the use of gender can enhance the safety of artificial kinematic replicators (Section 5.1.9 (L1)).

4.4 Artificial Biological Replicators (1965-present)

Schneiker[1012] reports that as long ago as 1965, the synthesis of life was publicly proposed as a national goal by professor Charles Price, then-president of the American Chemical Society. In 1967, the first synthesis of infectious viral PhiX174 DNA was reported by Goulian et al.[1858] In 1968 Taylor[1859] cited predictions that bacteria would soon be programmed. In 1970, Jeon et al[1860] reassembled an *Amoeba proteus* from its major components — nucleus, cytoplasm, and cell membrane — taken from three different cells, demonstrating the physical possibility of manually assembling biological replicators from more primitive parts. Morowitz[1861] suggested cooling cells to cryogenic temperatures in order to analyze and determine their structure. Artificial cells might then be assembled at such temperatures and set in motion by thawing. Morowitz also reported that microsurgery experiments on amoebas "have been most dramatic. Cell fractions from four different animals can be injected into the eviscerated ghost of a fifth amoeba, and a living functioning organism results." In 1972, Danielli[1862] described several possibilities for generating new lifeforms via genetic engineering and "life-synthesis."

In 1988, Richard J. Feldmann, NIH computer scientist and founder of Integrated Genomics Inc., argued that building a biological organism was a reasonable goal for the scientific community:[1863] "With exponentially increasing computer power, it will take far less than 80 years to be able to design and implement a biological system. The issue seems to be simply one of deciding we want to do a project like this, not the technological complexity of the project per se." Others[1723,1864] have more recently echoed this goal. By 2004, more than 100 laboratories were studying processes involved in the creation of life.[3107] "The ability to make new forms of life from scratch — molecular living systems from chemicals we get from a chemical supply store — is going to have a profound impact on society, much of it positive, but some of it potentially negative. Aside from the vast scientific insights that will come, there will be vast commercial and economic benefits, so much so that it's hard to contemplate in concrete detail what many of them will be," recently observed Mark Bedau,[3107] professor of philosophy and humanities at Reed College in Portland, Oregon, and editor-in-chief of the *Artificial Life Journal.*

Mushegian[1865,1866] examined the genes present in the genomes of fully sequenced microbes to see which ones are always conserved in nature. He concluded that as few as 256[1866] to 300[1865] genes are all that may be required for life, constituting the minimum possible genome for a functional microbe. (A comparable analysis by Fraser et al[1867] found a similar minimal number, 254 distinct essential proteins.) A single-cell organism containing this minimal gene set would be able to perform the dozen or so functions required for life — manufacturing cellular biomolecules, generating energy, repairing damage, transporting salts and other molecules, responding to environmental chemical cues, and replicating. Thus the minimal artificial microbe — a basic cellular chassis — could be specified by an artificial genome only 150,000 to 320,000 (assuming 1.25 kb/gene[1867]) nucleotide bases in length. By early 2000, Glen Evans had already produced made-to-order DNA strands up to 10,000 nucleotide bases in length[1868] and was striving to increase this length by at least a factor of ten (see below). For years, custom DNA and peptide sequences have been available for purchase online,[1869] and whole gene synthesis has been actively investigated at least since the mid-1970s[1870] and throughout the 1980s[1871-1873] and beyond.[1874]

An engineered full-genome DNA, once synthesized, could be placed inside an empty cell membrane — most likely a living cell from which the nuclear material had been removed. Used in medicine, these artificial biorobots could be designed to produce useful vitamins, hormones, enzymes or cytokines in which a patient's body was deficient, or to selectively absorb and metabolize into harmless end products harmful substances such as poisons, toxins, or indigestible intracellular detritus, or even to perform useful mechanical tasks — although natural biological systems appear incapable of true universal construction.[358-361] One private company, engeneOS,[1875] was formed in 2000 to pursue the construction of these artificial biological devices; in 2001 a nascent company, Robiobotics LLC,[1876] tried to put forward a business plan to pursue "whole genome engineering" and to seek funding; and physicist Norman Packard has established another company, ProtoLife,[3109] to capitalize on the new field of living technology: "The goal of the company is to realize the vision of producing living artificial cells, and also producing other forms of living chemistry, and then programming them to do useful chemical applications. The range of useful chemical functions we ultimately envision is vast," says Packard.[3107] Luisi[1877] has discussed top-down and bottom-up approaches to the engineering of synthetic minimal living cells, and several other groups may be even further along in wetware[1878] engineering. The European Union's Programmable Artificial Cell Evolution (PACE) project, recently established with a grant of about $9 million, was scheduled in March 2004 to open the first institution devoted exclusively to creating artificial life, called the European Center for Living Technology, in Venice, staffed by European and U.S. researchers, according to John McCaskill, professor of theoretical biochemistry at Friedrich-Schiller University in Jena, Germany, who is overseeing the European Union's artificial life program.[3107]

In November 2002, J. Craig Venter, of human genome-sequencing fame, and Hamilton O. Smith, a Nobel laureate, announced[1879] that their new company, Institute for Biological Energy Alternatives (IBEA), had received a $3 million, three-year grant from the Energy Department to create a minimalist organism, starting with the *M. genitalium* microorganism. Working with a research staff of 25 people, the scientists planned to remove all genetic material from the organism, then synthesize an artificial string of genetic material resembling a naturally occurring chromosome that they hoped would contain the minimum number of *M. genitalium* genes needed to sustain life.[1879] In this process, the artificial chromosome is inserted into the hollowed-out cell which is then tested for its ability to survive and reproduce. To ensure safety, Smith and Venter said the cell will be deliberately hobbled to render it incapable of infecting people; it also will be strictly confined and designed to die if it does manage somehow to escape into the environment.[1879] In late 2003, Venter reported the first fruits of this work — synthesis of the complete genome of a small (5386 base pairs) phi X bacteriophage virus in just 14 days.[1880]

In early 2003, Glen Evans' new company Egea Biosciences[1881] may have vaulted into the lead, having been granted "the first [patent][1132] to include broad claims for the chemical synthesis of entire genes and networks of genes comprising a genome, the 'operating system' of living organisms." According to the company, Egea's proprietary GeneWriter™ and Protein Programming™ technology has been validated in extensive proof of concept studies and has: (1) produced libraries of more than 1,000,000 programmed proteins, (2) produced over 200 synthetic genes and proteins, (3) produced the largest gene ever chemically synthesized of over 16,000 bases, (4) engineered proteins for novel functions, (5) improved protein expression through codon optimization, and (6) developed custom genes for protein manufacturing in specific host cells. Egea's software allows researchers to author new DNA sequences that the company's hardware can then manufacture to specification with a base-placement error of only ~10^{-4}, which Evans calls "word processing for DNA".[1882]

According to Egea's patent,[1132] one "preferred embodiment of the invention" would include the synthesis of "a gene of 100,000 bp ... from one thousand 100-mers. The overlap between 'pairs' of plus and minus oligonucleotides is 75 bases, leaving a 25 base pair overhang. In this method, a combinatorial approach is used where corresponding pairs of partially complementary oligonucleotides are hybridized in the first step. A second round of hybridization then is undertaken with appropriately complementary pairs of products from the first round. This process is repeated a total of 10 times, each round of hybridization reducing the number of products by half. Ligation of the products then is performed." The result would be a strand of DNA 100,000 base pairs in length, long enough to make a very simple bacterial genome.[1882] Evans says his prototype machine can link up 10,000 bases in two days, and that 100,000 bp strands might require "a matter of weeks" to synthesize using a future next-generation machine.[1882] "Pretty soon, we won't have to store DNA in large refrigerators," says Tom Knight. "We'll just write it when we need it."[1882]

The Synthetic Biology Lab at MIT[1883] is also investigating minimal organisms. One of their goals: "Dissect *Mesoplasma florum* and create a minimal organism. *Mesoplasma florum* is a Mycoplasma species with a genome size of 860,000 bp. It has been sequenced in collaboration with the Whitehead Institute and is being annotated. This organism was chosen because it is non-pathogenic, convenient to grow, and has a relatively small genome. The next step will be to build a minimal organism starting from this species by removing genes that are not needed and not well understood. The goal is to create a well-understood bare-bones organism to begin engineering in new desired functionality." A few of the many useful metabolic pathways that might be added have been compiled at the BioCyc website.[1884]

Mushegian's results[1865] suggest that the minimal autonomous artificial biological replicator consists of at least 300 different (protein) "nanoparts", multiple copies of each being assembled into a working biological robot. However, engineered replicators: (1) need not be designed for operation on diverse organic substrates, (2) need not be capable of self-assembly but may employ positional assembly techniques, (3) need not be capable of surviving mutation or evolution, and (4) need not contain (and by necessity maintain to high fidelity) their own description within their own onboard structure. Accordingly, Szostak et al[1885] have proposed a vastly simpler replicating protocell which would include principally an RNA replicase — an RNA molecule that can act both as a template for genetic information storage and transmission and as an RNA polymerase that can replicate its own sequence.[1886,2051] A single molecule cannot be both template and polymerase at the same time, so replication needs two RNA molecules:[1885] "A replicase that acts as the polymerase, and another molecule, which could be either an unfolded replicase or an RNA complementary in sequence to the replicase, to act as a template." The replicase (possibly 200-300 nucleotides in size) would replicate inside a replicating membrane vesicle, which would also contain a ribozyme that synthesizes amphipathic lipids (allowing membrane growth and maintenance). With these simplifications available to designers, it is likely that a positionally-assembled mechanical replicator can be at least as simple as Mushegian's minimal microbe and can possibly be designed using far fewer different kinds of parts than are found in this biological proof-of-concept. Similarly, there has been discussion of "chemical reaction automata" as precursors for synthetic organisms,[1887] synthetic lifeforms[1888] and "nanobiology",[1889] artificial cells[1890] and synthetic cell biology,[1891] lymphocyte engineering,[1892] microbial engineering,[1893-1898] cell surface engineering[1899-1901] and cell metabolic engineering.[1902-1907]

Engineered self-replicating bacteria are being pursued as gene delivery vectors by many research groups,[1908-1917] and also as anti-tumor agents, as for example by Vion Pharmaceuticals in collaboration with Yale University.[1918] In their "Tumor Amplified Protein Expression Therapy" or TAPET program,[1918] antibiotic-sensitive *Salmonella typhimurium* (food poisoning) bacteria were attenuated by removing the genes that produce purines vital to bacterial growth. The tamed strain could not survive very long in healthy tissue, but quickly multiplied 1000-fold inside tumors that are rich in purines. These engineered bacterial self-replicating machines were available in multiple serotypes to avoid potential immune response in the host, and Phase I human clinical trials were underway in 2002 using clinical dosages. The next step would be to add genes to the bacterium to produce anticancer proteins that can shrink tumors, or to modify the bacteria to deliver various enzymes, genes, or prodrugs for tumor cell growth regulation.

Such additions can include "unnatural" components. For instance, Schultz's group has engineered new strains of *E. coli* that can incorporate into bacterial proteins: (1) externally-supplied unnatural amino acids[1919] including p-azido-L-phenylalanine,[1920] the photocrosslinking amino acid p-benzoyl-l-phenylalanine,[1921] O-methyl-L-tyrosine,[1922] and L-3-(2-naphthyl)alanine,[1923] (2) unnatural amino acid functional groups such as keto groups,[1924] and even (3) non-amino acids such as alkenes.[1925] In 2003 Shultz's team reported[1926] the first creation of an *E. coli* strain that could not only incorporate but also internally synthesize another unnatural amino acid, *p*-aminophenylalanine — making, in essence, a completely autonomous bacterium having a 21 amino acid genetic code, including an artificial tRNA-synthetase/tRNA pair.[1927] Later in 2003, Shultz's team announced similar results for the first eukaryotic species, a type of yeast called *Saccharomyces cerevisiae*.[1928,1929]

Joseph Jacobson,[1930] scientific advisory board member for engeneOS, observes that a key to successful replication of complex biological systems is error correction. Biology employs many techniques for error correction. For example, protein coding uses fault-tolerant translation codes — e.g., in the genetic code of almost all organisms on Earth, polar residues are encoded by the "degenerate" (see below) DNA codon NAN, and non-polar residues are encoded by the degenerate codon NTN (where A = adenine, T = Thymine, and "N" denotes a mixture of DNA bases). Hecht[1931] reports that experiments with combinatorial libraries of de novo proteins show that sequences describing an alternating pattern of polar and non-polar amino acid residues (e.g., NANNTNNANNTN...) produce aggregative fibrillar structures resembling β-amyloid. This aggregation competes with (and may prevent) proper intramolecular folding, hence this pattern should be disfavored by evolutionary selection and in fact does occur significantly less often in the genome than other patterns with similar compositions.[1931] Another example is frameshift error tolerance, wherein two nonhomologous proteins may share the same DNA sequence — that is, reading the same sequence with a single base-pair frameshift may produce a second valid protein product.[1693] As yet another example, the entire genetic code is "degenerate" — that is, almost every amino acid is represented by several codons, with a slight tendency for more common amino acids to be represented by more codons.[1693] More importantly, this degeneracy minimizes the effects of mutations. A mutation of CUC to CUG has no effect, since both codons represent leucine; similarly, a mutation of CUU to AUU replaces leucine with isoleucine, a closely related amino acid.* [1693] The synthesis of proteins from amino acids by ribosomes (giant ribozymes) has an error rate of only one residue per 2,000 (error rate ~5 x 10^{-4}) largely due to mistaken tRNA recognition,[1693] which means that the majority of synthesized proteins (which average fewer than 1000 residues per protein) may include not a single error. DNA copying relies on extensive error detection and correction (e.g., presynthetic and proofreading error-correcting polymerases,[1932] thymine dimer bypass,[1933] base excision repair,[1934] base-pair mismatch correction systems[1935,1936]) along with built-in redundancy (the molecule has two complementary strands) to achieve a net error rate of only one base per billion (~10^{-9})[1693] when replicating itself.

"Error correction in biological systems has extremely high fidelity, but error is cumulative," notes Jacobson.[1930] "Can we create an organism which does not have cumulative error?" His solution, echoing the consensus-copy correction approach described in 1986 by Drexler (ref. 199, pp. 107-108), is to build living cells containing M duplicate strands of N bases per strand in a consensus voting system to create a self-excising error-correcting code. "For above [some] threshold M value [and] combining error correcting polymerase and error correcting codes, one can replicate a genome of arbitrary complexity," he claims. Similarly, the radiation-resistant bacterium *Deinococcus radiodurans* may preserve its genome following severe radiation damage in part by employing a high copy number of DNA.[1938,1939]

During the 1990s, bioengineered self-replicating viruses of various types[1940-1942] and certain other vectors routinely were being used in experimental genetic therapies as "devices" to target and penetrate certain cell populations, with the objective of inserting therapeutic DNA sequences into the nuclei of human target cells in vivo. Inserting new sequences into viral genomes, or combining components from two different viruses to make a new hybrid or chimeric virus,[1943,1951] is now routine. Efforts at purely rational virus design are underway but have not yet borne much fruit. For example, Endy et al[1944] computationally simulated the growth rates of bacteriophage T7 mutants with altered genetic element orders and found one new genome permutation that was predicted to allow the phage to grow 31% faster than wild type; unfortunately, experiments failed to confirm the predicted speedup. Better models are needed.[1891,1945] Nevertheless, combinatorial experiments on wild type T7 by others[1946-1948] have produced new but immunologically indistinguishable T7 variants which have 12% of their genome deleted and which replicate twice as fast as wild type.[1948] The Synthetic Biology Lab at MIT[1883] seeks to "build the next generation T7...a bacteriophage with a genome size of about 40,000 bp and 56 genes. With DNA synthesis becoming cheap, we wish to redesign and rebuild the entire genome, to create the next, and hopefully better, version of T7. Considerations in the redesign process include: adding or removing restriction sites to allow for easy manipulation of various parts, reclaiming codon usage, and eliminating parts of the genome that have no apparent function. Synthesizing a phage from scratch will allow us to better understand how Nature has designed the existing organism." Notes Endy:[3111] "We've rebuilt T7 — not just resynthesized it but reengineered the genome and synthesized that." The MIT scientists are separating overlapping genes, editing out redundancies, and so on, with about 11.5 kilobases completed so far and the remaining 30,000 base pairs expected to be completed by the end of 2004.[3111]

In a three-year project[1949] culminating in 2002, the 7500-base polio virus was rationally manufactured "from scratch" in the laboratory by synthesizing the known viral genetic sequence in DNA, enzymatically creating an RNA copy of the artificial DNA strand, then injecting the synthetic RNA into a cell-free broth containing a mixture of proteins taken from cells. The synthetic polio RNA then directed the synthesis of complete (and fully infectious) polio virion particles,[1949] allowing the researchers to claim that the virus was made without the use of any living cells. The rational design and synthesis of completely artificial viral sequences, leading to the manufacture of completely synthetic viral replicators, should eventually be possible — but the rational design and synthesis of chimeric viral replicators is already possible today.[1950-1952]

Attempts to create synthetic nonmicrobial biological replicators also are underway, For example, in 2000 Demin Zhou's group[1746] reported that they were trying to create a synthetic viroid consisting of "a naked RNA virus capable of infecting a cell, replicating, and modulating cellular function. The RNA molecule in the library is viroid-like, capable of rolling circle replication, self-splicing and ligation. Replication is performed by an RNA-dependent RNA polymerase (RdRp) that can replicate RNA by internal initiation on an RNA template. The designed circular RNA includes a ribozyme that leads to self-splicing and ligation, a promoter for an RdRp, an antisense sequence, and an infectivity site. We are now testing replication of the viroid by an RNA dependent RNA polymerase which has well defined activity in vitro and in vivo." It may also be possible to design artificial general-purpose bacteriophages that are capable of disabling or destroying all bacterial DNA, or are capable of replicating more bacteriophage particles to which only the targeted pathogenic bacterial cells are susceptible.[228,1757] Bacterial artificial chromosomes (BACs) and yeast artificial chromosomes (YACs) — essentially, synthetic plasmids — have been in wide use in biotechnology for years, e.g., as cloning vectors.[1953-1955] Chromosome engineering[1956] is beginning, and both mammalian artificial chromosomes (MACs)[1957] and human artificial chromosomes[1958] are actively being investigated. Rasmussen et al[1959] describe an organic artificial protocell that represents a simple self-replicating physicochemical system.

4.5 Biomolecular-Directed Positional Parts Assembly (1994-present)

The ability to positionally assemble nanoscale building blocks or nanoparts into larger nanomachines of various kinds is a key capability that could enable nanomachine self-replication. Several proposals have been made to harness the self-organizing abilities of polynucleotides, proteins, and even whole artificial microbes or viruses for this purpose. (The authors are also preparing an entire book[1] on the subject of nonbiological positional assembly with a focus on diamond mechanosynthesis; positional manipulator arrays are briefly described in Section 5.7.)

4.5.1 Positional Assembly Using DNA

Starting in 1994, Niemeyer[1451] and Smith[1417] exploited DNA specificity to generate regular protein arrays, using "oligonucleotide-directed self-assembly of proteins"[1451] and "nucleoprotein-based nanoscale assembly".[1417] Shi and Bergstrom[1960] attached DNA single strands to rigid organic linkers, showing that cyclical forms of various

---

** Each amino acid can be assigned a hydropathic index on the basis of hydrophobicity and charge characteristics,[1937] as follows: Isoleucine (+4.5), valine (+4.2), leucine (+3.8), phenylalanine (+2.8), cysteine/cystine (+2.5), methionine (+1.9), alanine (+1.8), glycine (-0.4), threonine (-0.7), serine (-0.8), tryptophan (-0.9), tyrosine (-1.3), proline (-1.6), histidine (-3.2), glutamate (-3.5), glutamine (-3.5), aspartate (-3.5), asparagine (-3.5), lysine (-3.9), and arginine (-4.5). Certain amino acids may be substituted by other amino acids having a similar (i.e., within 0.5-2 units) hydropathic index and still result in a protein with similar biological activity, i.e., still obtain a biologically functional-equivalent protein.[1132]*

sizes could be formed with these molecules. Working from the insight that DNA could serve as an assembly jig in solution phase, Smith and Krummenacker[1961] devised a possible method for the nanoassembly and covalent linkage of protein "nanoparts" into specific orientations and arrangements as determined by the hybridization of DNA attached to the proteins, called DNA-Guided Assembly of Proteins (DGAP).[1962] In this method, multiple DNA sequences would be attached to specific positions on the surface of each protein, and complementary sequences would bind, forcing protein building blocks (possibly including biomolecular motors, structural protein fibers, antibodies, enzymes, or other existing functional proteins) together in specific desired combinations and configurations, which would then be stabilized by covalent interprotein linkages. This technique could also be applied to non-protein components that can be functionalized at multiple sites with site-specific DNA sequences, although proteins, at least initially, may be more convenient building blocks due to their size, their surface chemistry, the wide variety of functions and mechanical properties they can confer on the resulting assemblies, and the many existing techniques for introducing designed or artificially evolved modifications into natural proteins of known structure. In 2001 a nascent company, Molecubotics, Inc., [1963] put forward a business plan to pursue the DGAP method of molecular assembly[1964] and to begin seeking funding.

Others are exploring methods for: covalently attaching functional (fusion) proteins to a DNA backbone in a specified manner at ~8.5 nm (25 base-pair) intervals;[1417] addressable protein targeting in macromolecular (e.g., nucleoprotein) assemblies;[1450-1457] attaching specific DNA tag sequences to protein molecules such as enzymes to a specific region on the surface of the target protein well away from the active site;[1965] laying of silver wire,[1966,2019] gold wire,[1967-1969] and other nanowires[1970-1974] using DNA as a molecular scaffolding or possible template for circuit construction,[1975] including metal-centered DNA lattices,[1976] metal nanoparticle assemblies,[1977,1978] and nanotube localization;[1979] decorating DNA with fullerenes[1980] and dendrimers;[1414] assembling DNA-tagged nanometer-sized gold,[1981,1982] magnetic,[1983] or other particles into larger clusters, or into spontaneous lattices[788] or magnetic chains;[1984] silicon component aggregation on DNA-directed 2-D array[1985] and "protein stitchery".[1986] Braun et al[1987] have used DNA scaffolding with several specific proteins as a template for the self-assembly of carbon nanotube based transistors, with metallic nanowires at either end. DNA self-assembly can sort mixed nanotubes into the metallic and semiconducting varieties.[1988] Cook et al[1989] show how DNA tiles can be used for self-assembled electronic circuit patterns and as a scaffold for functional devices such as molecular electronic circuits, and that several circuit patterns — such as demultiplexors, random-access memory, and Hadamard matrix transforms — can, in principle, be self-assembled from a small number of DNA tile types.

Seeman's group[1434-1450] at New York University has reported the design and construction of 2-dimensional DNA arrays (which might serve as templates for nanomechanical assembly)[1437,1441,1442,1990] and a mechanical DNA-based actuator[1436] (based on the solution-ion-based B-Z structural transition in DNA; Figure 4.23) and similarly actuated rotary motors[1434] and a bipedal nanowalker with 36 base-pair-long legs.[2342] Seeman is now collaborating[1991] with computational chemists to achieve "the design and fabrication of practical nanoscale devices" and "to make rapid progress in demonstrating DNA based nanoscale devices."* Erik Winfree at CalTech is investigating using DNA tiles to perform computing tasks.[1989,1992-1997]

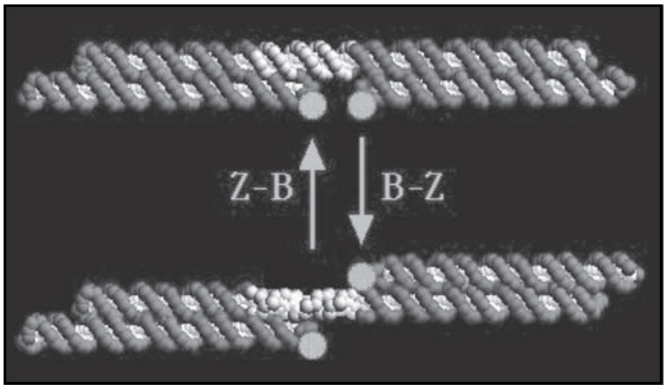


Figure 4.23. A mechanical DNA-based actuator. (courtesy of Nadrian Seeman[1436])

Other DNA-based actuation is known. For example, sequence-specific DNA hybridization is commonly used to bend silicon microcantilevers.[2002-2006] Alberti and Mergny[2010] synthesized a sequence-dependent DNA "piston" composed of a 21-base oligonucleotide that displays a 5-nm, two-stroke, linear motor type movement. Li and Tan[2011] have made a single-DNA-molecule inchworm motor. Shu and Guo[1754] synthesized a 30-nm long chimeric pRNA (DNA-packaging) motor made from six strands of RNA surrounding a center strand of DNA: in the presence of ATP, the RNA strands push the DNA axle in succession, spinning it around and producing 50-60 pN of force.

Researchers from Ludwig Maximilians University in Germany have built a simple molecular machine from DNA that can bind to and release single molecules of a specific type of protein.[3110] This "DNA hand" can be made to select any of many types of proteins, and could eventually be used to construct materials or machines molecule-by-molecule. "The researchers used DNA branch migration, a method that allows a DNA nanostructure to switch between several arrangements of its parts, to construct the DNA hand. In one configuration, the structure contains an open sequence of bases that binds to a specific protein, and so can grab that type of protein. A second configuration does not contain the open sequence, and so drops the protein. The rearrangements are reversible, allowing the tiny machine to repeatedly grab and drop a molecule of a specific type of protein. DNA aptamers, or strands that bind to specific molecules, can be selected from a pool of DNA sequences, making it possible to construct a DNA hand that binds to any type of protein."[3110] The DNA hand was demonstrated by having it repeatedly grab and drop molecules of the protein thrombin.

Bernard Yurke at Bell Laboratories and Andrew Turberfield at the University of Oxford have synthesized a sequence-dependent DNA-based actuator which has been cycled 7 times consecutively by inserting and removing a special "fuel" strand, causing the

---

** In a lecture at the 10th Foresight Conference in Washington DC in October 2002, Seeman noted that "self-replicating systems" are explicitly being studied by his research group, but that he "didn't have time for this today, the work is on hold for now." A lecture slide entitled "Challenges for structural DNA nanotechnology" included the item: "To produce systems capable of self-replication — economy; evolvability." Seeman has already built DNA-based nanomechanical devices[1434,1436] including "sequence-dependent devices [that] can provide the diversity of structures necessary for nanorobotics",[1998] and in 2002 Seeman wrote:[1999] "The development of **self-replicating systems** using branched DNA appears today to be somewhat oblique,[1450] but it nevertheless represents an exciting challenge that will significantly economize on the preparation of these systems and enhance their evolvability. Ultimately, structural DNA nanotechnology must advance from the biokleptic to the biomimetic, not just using the central molecules of life, but improving on them, without losing the inherent power they possess." According to Seeman in late 2003,[2000] the replication scheme, first presented in 1991,[1450] involves DNA knot topologies[2001] and requires the ability to characterize what is synthesized via direct structural observation, rather than by gel or other biochemical techniques; forthcoming 3-D arrays "make these systems amenable to crystallographic characterization before picking up the knot work again and then applying it to replication."*

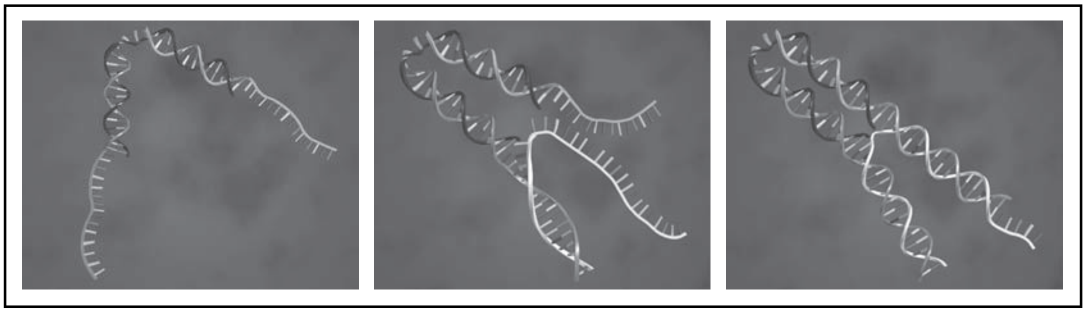


Figure 4.24. One half-cycle of Yurke's DNA-based actuator. (courtesy of Bernard Yurke[2012])

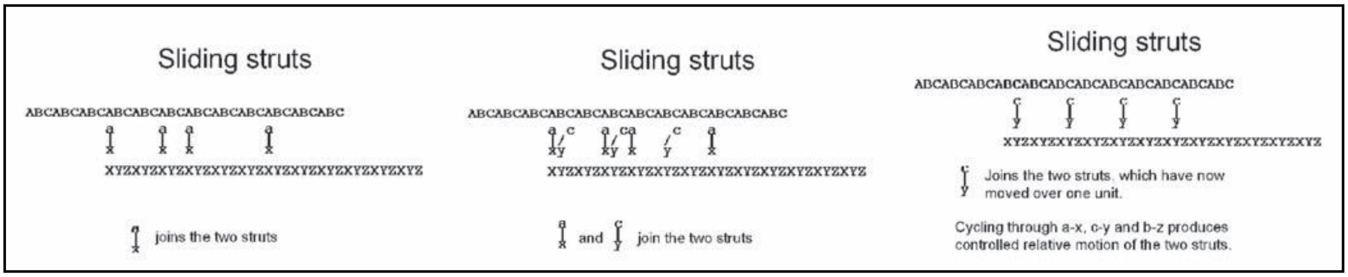

Sliding struts
ABCABCABCABCABCABCABCABCABCABCABCABC
XYZXYZXYZXYZXYZXYZXYZXYZXYZXYZXYZXYZ
joins the two struts
Sliding struts
ABCABCABCABCABCABCABCABCABCABCABCABC
XYZXYZXYZXYZXYZXYZXYZXYZXYZXYZXYZXYZ
and
join the two struts
Sliding struts
ABCABCABCABCABCABCABCABCABCABCABCABC
XYZXYZXYZXYZXYZXYZXYZXYZXYZXYZXYZXYZ
Joins the two struts, which have now moved over one unit.
Cycling through a-x, c-y and b-z produces controlled relative motion of the two struts.

Figure 4.25. Using reversible complementary linkers to actuate linear DNA-based strut in discrete steps. (from Merkle[2017])

"nanotweezer" to close from a ~7 nm separation to a ~1 nm separation (Figure 4.24), taking ~13 sec per cycle.[2012-2015] (More recent work[2016] has focused on a continuously running DNA nanomotor.) Merkle[2017] has proposed a similar chemically-driven DNA-based "sliding strut" actuator (Figure 4.25) which demonstrates that biotechnology and self-assembly can be used to make positional devices. Hao Yan and colleagues in Reif's lab at Duke University in Durham, North Carolina have devised X-shaped DNA tiles that link up in a square grid with some of the strands consisting of sections of DNA that can lengthen and shorten by 6.8 nm like tiny pistons, making a net whose mesh size can expand or contract under chemical control.[2018-2020] RNA polymerase has been utilized as a 15-20 pN positioning motor that "can be incrementally 'walked' or positioned along DNA with nanometer scale precision."[2021]

Reif[2022,2023] has designed (but not yet built) "the first autonomous DNA nanomechanical devices that execute cycles of motion without external environmental changes. These DNA devices translate along a circular strand of ssDNA [single-stranded DNA] and rotate simultaneously." Reif's first DNA device, called "walking DNA," would achieve random bidirectional motion around a circular ssDNA strand by using DNA ligase and two restriction enzymes that consume ATP as their energy source. Reif's second DNA device, called "rolling DNA," would achieve random bidirectional motion by using DNA hybridization energy in trapped states with no DNA ligase or restriction enzymes. The emerging field of DNA-based molecular construction appears quite active.[2024]

Mirkin's group[2025] has created 2-D and 3-D architectures with DNA and inorganic nanoscale building blocks, including using massively parallel tip arrays to write patterns using a DNA-based "ink".[2026] Mavroidis' group[71] is studying combining artificial DNA structures with carbon nanotubes (Figure 4.26). Jaeger and colleagues are investigating 9-13 nm self-assembling tectoRNA geometrical figures,[1675-1678] and von Kiedrowski's group[1429] has used synthetic three-armed tris-oligonucleotidyl building blocks to assemble 3-D DNA nanoscaffolds such as supramolecular tetrahedra. Others[2052] have tailored allosteric responses in ribozymes — capabilities which might also be useful in the context of positional nanoparts assembly. There have also been numerous experiments with artificial nucleic acids[2027] including unnatural nucleobases[2028-2030] and nucleosides[2031-2033] (e.g., thiophene and furan heterocycles), "universal" bases,[2034,2035] peptide nucleic acids (PNA),[2036-2038] threose nucleic acid (TNA),[2039] and extended (unnatural) genetic alphabets.[2040-2044]

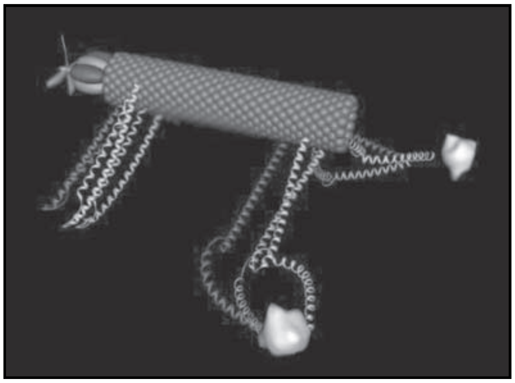


Figure 4.26. Theoretical proposal to combine biomolecular motor molecules and artificial DNA structures with carbon nanotubes (courtesy of Constantinos Mavroidis[71]). This "artist's conception" is only schematic and somewhat fanciful, as components are not all shown to scale.

4.5.2 Positional Assembly Using Proteins

Bradbury[2045] proposes using artificial enzymes for nanoscale parts assembly. After noting Merkle's[2017] suggestion that the positional control of nanoscale building blocks would allow the extension of the normal reactions found in biological systems to include free-radical chemistry and more recent descriptions of similar reactive chemistries being employed by enzymes,[2046] and related informal suggestions for artificial mechanoenzymes by Freitas[2047] and "mechalysts" by Craver,[2048] Bradbury[2045] envisioned the engineering of artificial multifunctional proteins called "robozymes" having the following properties: (1) unfolded, the robozyme grabs onto molecular building blocks,[2088-2090] carefully keeping them separate from each other to avoid nonspecific reactions; (2) using specific enzyme catalytic sites near the bound building blocks, it "activates" the molecules (perhaps producing one or more free radicals); (3) induced folding brings the building blocks into relatively precise alignment allowing the desired chemical reaction(s) to occur; and (4) the protein is induced to unfold, releasing the final product. With protein folding forces in the tens to hundreds of pN, such enzymes could also provide a means for threading one molecule through another molecule, mechanically producing interlinked structures such as rotaxane and catenane[1516] without using self-assembly (i.e., by adding hydrophobic ring structures to the molecular parts which will then be attracted to each other in a polar solvent like water) and thus allowing the positional assembly of very small (<1 kD) molecular nanoscale parts.

Note that while most enzymes in cells are involved in manipulating small molecules <0.25 kD, there are several classes of enzymes involved in manufacturing complex covalently bound molecules such as vitamins, enzyme cofactors, antibiotics, and toxins with masses up to ~3 kD. Molecules even larger than this are manipulated by tRNA-synthetase (a 40-100 kD enzyme that manipulates ~30 kD tRNAs), the spliceosome, the ribosome, the proteosome, and the DNA replication complex. (Many of these also involve "parts insertion" or "threading" maneuvers, such as the clamp and bridge helix mechanisms in RNA polymerase II that act as a translocation ratchet to feed DNA through the enzyme interior in order to produce mRNA.)[2049] By designing synthetic enzymes consisting of synthetic amino acids, we can envision grabbing molecular parts in a solution and then, as the enzyme folds, bringing them into proper alignment and causing them to react — which might be called "nanopart synthetases" or "protein-directed parts assembly." Of course, RNA-based ribozymes[2050-2054] may prove better suited than proteins for some reactions, so we are not limited to using enzymes to form the covalent bonds required in nanoparts. Directed evolution in bacteria might be employed to create such specialty enzymes — as has already been done, for example, in converting a disulfide reductase (disassembly) enzyme into a disulfide-forming (assembly) enzyme.[2055]

Ratchet-action protein-based molecular motors are well-known in biology.[2056] Conformational cascades of a special genetic variant of yeast cell prions have already been used to self-assemble silver- and gold-particle-based nanowires.[2057,2058] The GTPase dynamin mechanoenzyme — which self-assembles into rings or spirals, wrapping around the necks of budding vesicles and squeezing, pinching them off, during cellular endocytosis — is well-known.[2059-2063] Amyloid fibril lamination can be exploited for nanotube self-assembly,[2064] and artificial self-assembled peptides can orient carbon nanotubes (CNTs) into fibers,[2065] achieve hydroxyapatite crystallization,[2066,2067] or grow copper nanocrystals.[2068] Smith[1153,2069] has used methyltransferase-directed addressing of fusion proteins to DNA scaffolds to construct a molecular camshaft (Figure 4.27) as a exemplar protein/nucleic acid biostructure. Bachand and Montemagno[2070] have engineered a biomolecular motor constructed of F1-ATPase protein[2071] with an attached silicon nitride "propeller" arm[2072] and a reversible on/off switch,[2073] and other task-optimized genetically engineered molecular motors have been synthesized by others.[2074] Protein-protein binding specificity has been used to bend silicon microcantilevers.[2002,2004,2007] Finally, molecular chaperones are a group of proteins that assists in the folding of newly synthesized proteins or in the refolding of denatured proteins. Genetically engineered chaperonin protein templates (heat shock proteins serving as chaperone molecules) can direct the assembly of gold (1.4, 5, or 10 nm) and CdSe semiconductor quantum dots (4.5 nm) into nanoscale arrays.[2075]

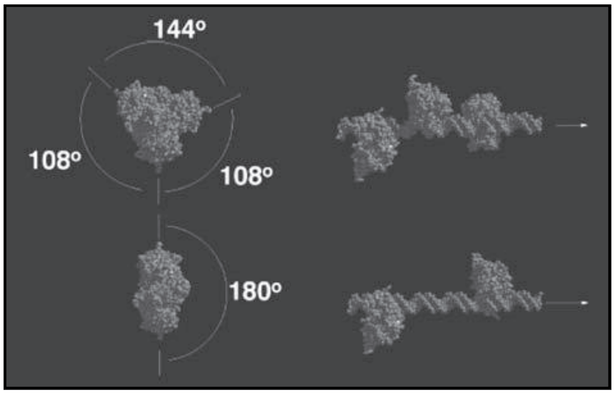


Figure 4.27. Self-assembled protein/nucleic acid molecular camshaft, in 3-lobe (above) and 2-lobe (below) versions. (courtesy of Steven S. Smith[2069])

Immunoglobulin (Ig) or antibody molecules could be used first to recognize and bind to specific faces of crystalline nanoparts, then as handles to allow attachment of the parts into arrays at known positions, or into even more complex assemblies. As reported by Freitas[235] (next 3 paragraphs): Kessler et al[2076] raised monoclonal antibodies (MAbs) specific for crystals of 1,4-dinitrobenzene having well-defined molecular-level structures. These antibodies were so specific they would not bind to the same molecule when it was conjugated to a protein carrier. IgG antibodies isolated from the serum of rabbits injected with crystals of monosodium urate monohydrate or magnesium urate octahydrate evidently bear in their binding sites an imprint of the crystal surface structure because they can act as nucleating templates for crystal formation in vitro with extremely low cross-reactivity, despite the similar molecular and structural characteristics of the two crystals.[2077] Antibody binding to monosodium urate crystals has been known for decades,[2078] and viruses have been engineered with a specific recognition moiety for ZnS nanocrystals used as quantum dots.[2160] Interestingly, antibodies specific to in vivo water-ice crystals have even been reported.[2079]

Like antigens with ordered multiple epitopes (the antigenic determinants), crystals expose chemically and geometrically distinct surfaces, so different antibodies might recognize distinct faces of a crystal (possibly including diamond or sapphire crystal faces) in an interaction similar to that of antibodies for repetitive epitopes present on protein surfaces.[2080,2090] For instance, one MAb to 1,4-dinitrobenzene crystals was shown to specifically interact with the molecularly flat, aromatic, and polar (101) face of these crystals, but not with other faces of the same crystal.[2088] MAbs have also been elicited against cholesterol monohydrate crystals,[2081,2082] one of which[2081] was shown to specifically recognize the crystal's stepped (301) face. Here, the hydrophobic cholesterol hydrocarbon backbone is exposed on one side of the molecular steps while hydroxyl residues and water molecules are exclusively exposed on the other side. In both cases, crystal-specific antibodies were of the IgM idiotype.[2090] This accords with the assumption that (unlike most commonly used antigens) crystals cannot be processed by the antigen presenting cells, hence antibodies must be induced through a T cell-independent path.[2083] Semiconductor-binding[2160,2163] and calcite-binding[2084] proteins are known that can discriminate among the various crystal faces of the given material and can in some cases alter the pattern of crystal growth.[2085] Sulfur-free gold-binding proteins (GBPs) recognize and noncovalently bind preferentially to the Au (111) crystal surface — GBPs use multiple repeats of 14-30 residue sequences to bind to this surface.[2086] Hyaluronan is believed to be a crystal-binding protein for calcium oxalate monohydrate crystals.[2087]

Solubilized (derivatized) C_{60} and C_{70} fullerenes can induce the production of specific antibodies,[2089-2093] usually by interaction with the combining sites of IgG.[2089] It is speculated that highly hydrophobic pure fullerenes would be recognized by antibodies with hydrophobic amino acids in their binding sites[2089,2094] or would interact with donor $-NH_2$[2098] and -SH[2099] groups. There are now many reports of antibodies being raised to single-walled carbon nanotubes.[2093-2097] For example, antibodies raised to C_{60} in mice strongly bind to single-walled nanotubes.[2097] Computer simulations suggest that it may be possible to build antibodies that selectively bind to nanotubes of a specific diameter or chirality.[2094]

4.5.3 Positional Assembly Using Microbes and Viruses

Artificial microbes (Section 4.4) might also be employed in molecular construction. A variety of biological molecular machines are already known which display linear motions, movements related to opening, closing and translocation functions, rotary movements, and threading-dethreading movements.[2100] Gerald J. Sussman at MIT claims that when computer parts are reduced to the size of single molecules, engineered microbes could be directed to lay down complex electronic circuits.[2101] "Bacteria are like little workhorses for nanotechnology; they're wonderful at manipulating things in the chemical and ultramicroscopic worlds," he says. "You could train them to become electricians and plumbers, hire them with sugar and harness them to build structures for you."

Regarding microbe-directed parts fabrication, one strain of bacteria (*Pseudomonas stutzeri AG259*) is known to fabricate single crystals of pure silver in specific geometric shapes such as equilateral triangles and hexagons, up to 200 nm in size.[2102,2103] Several anaerobic bacteria grow 300-nm nanosphere shells outside their cell envelopes,[2104] and microorganisms can accumulate materials and synthesize inorganic structures composed of bismuth,[2105] CdS,[2106,2107] gold,[2109] magnetite,[2107,2110] selenium,[2104] silica,[2107] and silver.[2107,2108]

As for microbe-directed parts assembly, Kondo et al[2111] used a grooved film (created by chemically precipitating cellulose tracks less than 1 nm apart onto a copper base) to induce the bacterium *Acetobacter xylinum* to exude neat ribbons of cellulose[2112] along the prepared track at a rate of 4 microns/minute. The group is attempting to genetically modify the organism to secrete alternative sugar molecules that might better resist natural degradation. Natural fibroblasts in human tissue construct complex 3-dimensional collagenous fiber networks of extracellular matrix (ECM) during wound healing,[2113] fibrillogenesis[2114] and fibroplasias.[2115] Although ECM strand positioning is stochastic in natural fibroblasts,[2116] cell functionality and ECM network characteristics can be altered by chemotactic factors,[2117,2118] contact guidance and orientation,[2119] hypoxia,[2120] and local mechanical stress.[2121] Fibroblasts can be genetically engineered,[2122] are capable of crosslinking collagen fibers[2123] (a "covalent parts joining" type of operation), and can apply ~100 pN forces while embedded in a 3-dimensional collagen lattice.[2124]

To establish digital control over microorganisms, genetic circuits that can function as switches[2125] or computational logic elements such as AND, NAND, and NOR gates (*Nanomedicine*,[228] Section 10.2.3.1) are under active investigation.[2126-2141] For example, in 2000 Gardner et al[2130] added a memory device to an *E. coli* bacterium using two inverters for which the output protein of each is the input protein of the other. Elowitz and Leibler[2129,2133] made an oscillator with three inverters connected in a loop — in one test of their "Repressilator" system, "a fluorescent protein became active whenever one of the proteins was in its low state....the result was a population of gently twinkling cells like flashing holiday lights."[2137] By 2002, Weiss[2139-2143] had created a five-gene circuit in *E. coli* that could detect a specific chemical in its surroundings and turn on a fluorescent protein when the chemical concentration enters within preselected bounds.[2137]

The Synthetic Biology Lab at MIT is similarly trying to create cells that are "engineered genetic blinkers"[2144] and which use light as a faster means of cellular I/O than chemical-mediated signals.[1883] They are also creating a set of "BioBricks"[1883,2145] which are "a [standardized] set of [building block] components that have been designed for use as logic functions within a cell. The members of this family are designed to be compatible, composable, interchangeable, and independent so that logic circuits may be constructed with little knowledge or concern for the origins, construction, or biological activities of the components." These components are being accumulated in M.I.T.'s Registry of Standard Biological Parts,[2145] an online database that by June 2004 listed distinct 517 parts or devices, with the number growing by the month. Boston University bioengineer and Cellicon Inc. founder and Senior Scientist Timothy Gardner explains[2137] that the eventual goal "is to produce genetic 'applets', little programs you could download into a cell simply by sticking DNA into it, the way you download Java applets from the Internet." Bacterial memory has also been demonstrated: 150-base-long messages encoded as artificial DNA have been stored within the genomes of multiplying *E. coli* and *Deinococcus radiodurans* bacteria and then accurately retrieved.[2146] Unfortunately, notes Weiss:[3111] "Replication is far from perfect. We've built circuits and seen them mutate in half the cells within five hours. The larger the circuit is, the faster it tends to mutate."

External control has been shown experimentally. Jacobson's team[2147] has demonstrated remote electronic control over the hybridization behavior of DNA molecules by inductive coupling of a GHz radio-frequency magnetic field to a 1.4 nm gold nanocrystal covalently linked to DNA,[2147] offering the prospect of remote-controlled enzymes and "radio-controlled bacteria".[2148] Single-molecule heating of bioconjugable gold nanowires, nanocircles and nanocoils is also being investigated by the von Kiedrowski group.[2149]

Bacteria can also be used as physical system components. For example, Tung et al[2150,2151] are attempting to incorporate living bacteria into microelectromechanical systems (MEMS) to form living cell motors for pumps and valves. The bacteria will be completely sealed inside the bioMEMS device. "When its flagellum is attached to a surface, the bacterium moves in a circular fashion, and always in the same direction,' explains Tung.[2151] "A single bacterium can become a flagellar motor or pump, but a number of bacteria, all rotating in the same direction, could become a conveyor belt." However, Tung[2152] notes that unlike ATPase which can potentially be assembled from proteins, flagellar motors cannot yet be artificially manufactured so the replication techniques developed for ATPase may not be applicable to flagellar motors. Smith[2153] also notes that it is presently unknown how to synchronize the rotational directions of multiple flagella in the lab.

Similarly, Linda Turner and colleagues at the Rowland Institute at Harvard have affixed a film of *Serratia marcescens* bacteria onto tiny beads, allowing the microbes' rotating appendages to carry the beads along. When the film is applied inside tiny tubes, the gyrating bacterial arms blend fluids twice as fast as diffusion alone.[2154] Carlo Montemagno at UCLA has combined living cells with isolated MEMS structures to create cell-powered mechanical motors. In one experiment in 2003, a lithographically-produced U-shaped structure 230 microns wide is attached to a cardiac muscle cell like a tiny prosthesis. When presented with glucose solution, the muscle cell contracts repeatedly, causing the mechanical structure to "walk" at a speed of ~46 microns/min with a repetition rate controlled by the spring constant of the MEMS structure.[2155] Sequeira and Copik[2156,2157] once proposed using bacteria as power units for microscale mechanical systems.

Viral shells also can provide useful templates for nanoscale assembly. Belcher[1435,2158-2163] employs virus capsid shells as temporary scaffolds for the directed nanoassembly of nanoparticles such as quantum dots,[2168] CoPt and FePt nanowires,[2161] and ~30 other inorganic semiconducting or magnetic materials in a process she describes[2158] as the "biomimetic synthesis of nonbiological inorganic phases with novel electronic and magnetic properties directed by proteins and synthetic analogs." In one experiment,[2160] a genetically engineered M13 bacteriophage with a specific recognition moiety for zinc sulfide nanocrystals was used to assemble a ZnS-containing film having nanoscale ordering and 72-micron-sized domains. Belcher and Hu have formed a company, Senzyme, to commercialize this process. Viral coat proteins can be engineered by various techniques[2169] and have been used by others as scaffolds for nanomaterials synthesis,[2170,2171] in self-assembly[2172] (e.g., of viral capsid monolayers on gold surfaces[2173]), and for encapsulation of reactants or polymers inside viral capsid cage structures.[2174]

4.5.4 Positional Assembly Using Other Biological Means

Drum and Gordon[2175] note that "diatom nanotechnology," first proposed in 1988,[2176] might be used to produce useful structures "by compustat selection experiments (i.e., forced evolution of development or evodevo). Their exponential growth in suspension cultures could compete with the lithography techniques of present day nanotechnology, which have limited 3-D capabilities. Alternatively, their fine detail could be used for templates for MEMS, or their silica deposition systems isolated for guiding silica deposition." Artificial diatom patterns were first synthesized via 3-D vapor deposition of silica by Shultze[2177] and others.[2178] Diatoms in the shapes of ~10-20 μm rectangular and triangular prisms are well-known.[2175] Diatom shells placed in a magnesium gas atmosphere at 900 °C for 4 hours undergo an atom for atom substitution of Mg for Si with no change in 3-D shape, and the authors list nine other "shape preserving gas/solid reactions" that are thermodynamically favored, and should "replicate" silica diatom shells in other oxide materials.[2179]

Drum and Gordon see two major advantages: "Large numbers of components are available via the exponential reproduction of the organisms that produce them, and mutation permits us to selectively evolve organisms with the components we want." Diatoms have a ~24 hour cell cycle, so their numbers can double every day. Gordon's "compustat" technique is "basically a selective breeding and culling of microorganisms based on shape. The idea was to do it visually by growing diatoms in a chamber with an image coming through a microscope to a computer. The computer would find each cell in turn and compare it with an ideal that you'd like to achieve. If the cell was anywhere near that ideal you'd leave it alone and if it wasn't, you'd kill it by zapping it with a laser."[2180] Projected uses include sensors, optical gratings, catalytic substrates, and even nanoscale comb actuators.[2175]

Sponges can also form solid silica structures with precisely controlled morphologies, directed by proteins and polysaccharides. For example, silicatein-a protein found in the silica spicules of the sponge *Tethya aurantia* can hydrolyze and condense the precursor molecule tetraethoxysilane to form silica structures with controlled shapes, including hard silica spheres and well-defined columns of amorphous silica.[2181]

4.6 Feynman Hierarchical Machine Shop (1959) and Microassembly

In his famous December 1959 speech, "There's Plenty of Room at the Bottom," Nobel physicist Richard P. Feynman[2182] observed that: "The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but, in practice, it has not been done because we are too big." Feynman then proposed the prototypical top-down strategy for building complex nanomachinery — essentially a completely teleoperated machine shop, including mills, lathes, drills, presses, cutters, and the like, plus master-slave grippers to allow the human operator to move parts and materials around the workshop.

To build a nanomachine using Feynman's scheme,[2182,2183] the operator first directs a macroscale machine shop to fabricate an exact copy of itself, but four times smaller in size. After this work is done, and all machines are verified to be working properly (and as expected), then the reduced-scale machine shop would be used to build a copy of itself, another factor of four smaller which is a factor of 16 tinier[2182] than the original machine shop. This process of fabricating progressively smaller machine shops proceeds until a machine shop capable of manipulations at the nanoscale is produced.* The end result is a nanomachine shop capable of reconstructing itself, or of producing any other useful nanoscale output product stream that is physically possible to manufacture, using molecular feedstock. As Feynman describes the idea, which includes massive parallelization:[2182]

> *"If you work through a pantograph, even today, you can get much more than a factor of four in even one step. But you can't work directly through a pantograph which makes a smaller pantograph which then makes a smaller pantograph — because of the looseness of the holes and the irregularities of construction. The end of the pantograph wiggles with a relatively greater irregularity than the irregularity with which you move your hands. In going down this scale, I would find the end of the pantograph on the end of the pantograph on the end of the pantograph shaking so badly that it wasn't doing anything sensible at all. At each stage, it is necessary to improve the precision of the apparatus. If, for instance, having made a small lathe with a pantograph, we find its lead screw irregular — more irregular than the large-scale one — we could lap the lead screw against breakable nuts that you can reverse in the usual way back and forth until this lead screw is, at its scale, as accurate as our original lead screws, at our scale.*
>
> *"When I make my first set of slave hands at one-fourth scale, I am going to make ten sets. I make ten sets of hands, and I wire them to my original levers so they each do exactly the same thing at the same time in parallel. Now, when I am making my new devices one-quarter again as small, I let each one manufacture ten copies, so that I would have a hundred hands at the 1/16th size....If I made a billion little lathes, each 1/4000th the scale of a regular lathe, there are plenty of materials and space available because in the billion little ones there is less than two percent of the materials in one big lathe. It doesn't cost anything for materials, you see. So I want to build a billion tiny factories, models of*

** Perhaps Feynman himself was partly inspired by the children's book "The Cat in the Hat Comes Back," published one year earlier in 1958 by Dr. Seuss,[2184] wherein a conceptually similar progressive system of manipulators is described, disguised as a young person's primer on the alphabet. The story line: While the kids are stuck shoveling snow, the laughing Hat Cat lets himself in the house and eats a pink cake in the bathtub. He leaves behind "a big long pink cat ring," which he then handily cleans with "MOTHER'S WHITE DRESS!" The dress then loses its pink stain to the wall, and then to "DAD'S $10 SHOES!", the rug in the hall, and then to the bedspread, until finally the Hat Cat calls in some assistants. From inside his big hat comes Little Cat A, then progressively smaller Little Cats B, C, D, and E, each nested in the previous one's hat, and so on down to Little Cat Z, who "is too small to see." The Little Cats make things worse, spreading the pink stain all over the front yard snow. The mess is finally cleared by Little Cat Z who has an even smaller, mysterious "Voom" in* his *hat, described only as "so hard to get" but "cleans up anything." The Hat Cat orders Cat Z to "Take the Voom off your head! Make it clean up the snow!" Acting like a janitorial utility fog (Section 3.8), spiraling clouds spin through the yard; in a whirlwind of action, all the pink is gone. Exclaims the relieved child: "Don't ask me what Voom is. I never will know. But, boy! Let me tell you. It DOES clean up snow!" The whirling fog also leaves behind a perfectly shoveled path from the street sidewalk to the front door, sparing the kids any further work.*

> *each other, which are manufacturing simultaneously, drilling holes, stamping parts, and so on.*
>
> *"As we go down in size, there are a number of interesting problems that arise. All things do not simply scale down in proportion. There is the problem that materials stick together by the molecular (van der Waals) attractions. There will be several problems of this nature that we will have to be ready to design for....[But] if we go down far enough, all of our devices can be mass produced so that they are absolutely perfect copies of one another. We cannot build two large machines so that the dimensions are exactly the same. But if your machine is only 100 atoms high, you only have to get it correct to one-half of one percent to make sure the other machine is exactly the same size — namely, 100 atoms high!"*
>
> *"Our ability to see what we are doing, and to do things on an atomic level," Feynman concluded, "is a development which I think cannot be avoided."*

To help motivate progress in top-down mechanical engineering, in his 1959 lecture[2182] Feynman also issued two seemingly "impossible" challenges: (1) to build a working electric motor no larger than a 1/64th-inch cube, and (2) to write a page of a book on an area 1/25,000 times smaller in linear scale "in such manner that it can be read by an electron microscope," each challenge backed by a $1000 prize. Just 11 months later, engineer William McLellan had constructed a 250-microgram 2000-rpm motor out of 13 separate parts that would fit inside a 0.4-mm cube, and collected his reward against the first challenge.[2185] (The second prize was won in 1985 by Tom Newman, who used e-beam lithography (Section 4.7) to meet the second challenge by writing the first page of Dickens' *A Tale of Two Cities* legibly in a 6.25-micron square, taking about 60 seconds).* [2185]

The field of micromechanical engineering gathered momentum after lithographically-produced silicon-chip-based working micromotors were fabricated in the late 1980's by groups at Berkeley and MIT. By 1990, tiny electrostatic motors with 100-micron rotors boasted operating speeds of ~250 Hz[2186] and operating lifetimes of ~10^6 revolutions.[2187] Wobble micromotors such as those fabricated in silicon by the University of Utah's micromachine lab demonstrated very little friction or abrasion, with measured operating lifetimes in excess of 300 million revolutions.[2188] Microelectromechanical or "MEMS" research has since produced multi-micron-scale accelerometers,[2189-2191] diverse microsensors (e.g., blood pressure microsensors attached to cardiac catheters), microscale cantilevers and jointed crank mechanisms,[2192] 5-micron barbs,[2193] flow microvalves and pressure microtransducers,[2194,2195] micropistons and micropumps,[2195] microgear trains,[2196] microactuators,[2197] piezo-driven micromotors,[2198] micromirrors and microshutters,[2199-2201] Fresnel lens microarrays,[2202] microgyroscopes,[2203] a 2-mm long combustion chamber suitable for turbine use,[2204,2205] and multidevice microsystems[2206] that were available customized or off-the-shelf in mass quantities by the late 1990s. MEMS had also produced microgrippers that could manipulate individual 2.7-micron polystyrene spheres, dried red blood cells of similar size, and various protozoa.[2207]

Could these microscale components be assembled into complex machines? Very simple mobile robots of ~1 cm^3 volume were commonplace in the 1990s,[2208-2211] so for a more challenging demonstration of MEMS' ability to manufacture complete working microrobots, in 1994 Japanese researchers at Nippondenso Co. Ltd. fabricated a 1/1000th-scale working electric car.[2212,2213] As small as a grain of rice, the micro-car was a 1/1000-scale replica of the Toyota Motor Corp's first automobile, the 1936 Model AA sedan. The tiny vehicle incorporated 24 assembled parts, including tires, wheels, axles, headlights and taillights, bumpers, a spare tire, and hubcaps carrying the company name inscribed in microscopic letters, all manually assembled using a mechanical micromanipulator of the type generally used for cell handling in biological research. In part because of this handcrafting, each microcar cost more to build than a full-size modern luxury automobile. The Nippondenso microcar was 4.8 mm long, 1.8 mm wide, and 1.8 mm high, consisting of a chassis, a shell body, and a 5-part electromagnetic step motor measuring 0.7 mm in diameter with a ~0.07-tesla magnet penetrated by an axle 0.15 mm thick and 1.9 mm long. Power was supplied through thin (18 micron) copper wires, carrying 20 mA at 3 volts. The motor developed a mean torque of 7×10^{-7} N-m (peak 13×10^{-7} N-m) at a mean frequency of ~100 Hz (peak ~700 Hz), propelling the car forward across a level surface at a top speed of 10 cm/sec. Some internal wear of the rotating parts was visible after ~2000 sec of continuous operation; the addition of ~0.1 microgram of lubricant to the wheel microbearings caused the mechanism to seize due to lubricant viscosity. The microcar body was a 30-micron thick 20-milligram shell, fabricated with features as small as ~2 microns using modeling and casting, N/C machine cutting, mold etching, submicron diamond-powder polishing, and nickel and gold plating processes. Measured average roughness of machined and final polished surfaces was 130 nm and 26 nm, respectively. The shell captured all features as small as 2 mm on the original full-size automobile body. Each tire was 0.69 mm in diameter and 0.17 mm wide. The license plate was 10 microns thick, 0.38 mm wide and 0.19 mm high.

Nippondenso subsequently used similar manufacturing techniques to build a prototype of a capsule intended to crawl through tiny pipes in a power plant or a chemical plant like an inchworm,[2214] hunting for cracks,[2215,2216] and other miniature mobile robots have been announced.[2217,2218] In 1999, three Japanese electronics companies revealed the creation of a 0.42-gram, 5-mm long "ant-size" robot[2219] reportedly able to lift 0.8-gm loads and move at ~2 mm/sec, as part of the government's ongoing Micro Machine Project.[2220] In early 2003, James Ellenbogen announced[2221] that researchers at MITRE Corp. were constructing a motorized silicon chip with 6 legs as a prototype millimeter-size robot or "millibot", to demonstrate control engineering with coordinated walking and obstacle avoidance by 2004. Kristofer Pister's group at UC Berkeley is working on millimeter-scale "smart dust with legs" and a micro rocket project, the details of which are not publicly available.[2222] In late 2003, Ebefors[2223] had the closest to a working walking microrobot.

What about Feynman's vision of a progressively miniaturized factory? Fearing et al[1582,2224] at UC Berkeley "plan to build a self-contained desktop rapid prototyping system" combining folding, bonding, and microassembling operations on 100-micron-scale parts to make a fully-automatic, desktop assembly process for millirobots, as part of their laboratory's NSF-supported Desktop Rapid Prototyping Millirobots project[2225] and their interest in automated microassembly[2226] — though oriented to "minimal bootstrapping for millirobot desktop factories, rather than self-replicating".[2227] The Agile Assembly project at Carnegie Mellon University[2228,2229] is developing an "agile assembly architecture" applied specifically to tabletop-sized factories or "minifactories" for microassembly including modular elements such as high-precision platens, bridges for mounting modular robotic elements, precision

---

* *Regis[2185] reports that a publisher of Buddhist texts subsequently contacted Newman to ask if he had any interest in creating a line of microscopic prayer books. Explained the publisher: "Miniature texts have potential ritual uses that are very intriguing. One requirement would be that the texts be in Tibetan script, rather than the standard Roman alphabet, but we already have or could modify a bit map of the Tibetan alphabet."*

2-DOF manipulators, 2-DOF couriers, and parts feeders, with the assembly of high-density mechatronic equipment as the prototypical application. (See also Section 3.20.)

Ongoing research efforts in precision or automated microassembly, desktop manufacturing,[2230,2231] microfactories[2232,2233] and parallel micromanufacturing are currently in progress at the Agency of Industrial Science and Technology, AIST (Mechanical Engineering Laboratory),[2232] Carnegie Mellon University (Microdynamic Systems Laboratory[2228] and Robotics Institute),[2234] European IST Program (MiCRoN Project),[2235] Innovation On Demand, Inc.,[2236,2237] Institute for Machine Tools and Industrial Management (Munich Microassembly Research),[2238] Lawrence Livermore National Laboratory (Micro Assembly Automation Laboratory),[2239] Nagoya University (Department of Micro System Engineering),[2240] Nelson's group,[2241,2242] Rensselaer Polytechnic Institute (Center for Automation Technologies),[57] Sandia National Laboratories (Precision Micro Assembly Laboratory),[2243] University of California at Berkeley (Robotics and Intelligent Machines Laboratory),[2244] University of Minnesota (Advanced Microsystems Laboratory),[2245] USATU (Center of High Technologies in Manufacturing Systems),[2246] Zyvex Corp. (Assembly of Microsystems),[2247,2248] and elsewhere.[2249-2252]

4.7 Shoulders Electronic Micromachining Replicator (1960-1965)

In 1960-1965, the controversial inventor K.R. Shoulders[2253-2256] speculated on a completely electronic-mediated mode of replication that envisioned manipulation of physical materials:

> *In the simplest case, the machine should be an iterative array of components that are isolated from each other, but have the ability to intercommunicate via sinuous electron paths. The components must be able to launch, adsorb, receive and steer electrons or groups of electrons. Such an organization would allow the creation of order within the machine at the dictate of other organized areas. This newly-made order could be propagated physically through the machine and then be destroyed if found wanting. The components could then be used again for higher levels of organization. This arena concept (using fundamental elements at fixed or movable loci but having flexible connectivity and a reversible change of state without leaving a residue) would greatly modify most present concepts of machine organization.... We will claim that field-emission devices could be used to fabricate a 'wireless' machine using any interesting organization...and that a complete machine could be built on this principle.*
>
> *We propose a component based upon the quantum-mechanical tunneling of electrons into the vacuum. Ultimately, we would use a vacuum-tunnel effect cathode array for our electron source. The emission from discrete areas would be controlled by local grids. Thus we have components made by electronic micromachining responsible for the building of new systems by the same method. In the end, self-reproduction would be a distinct possibility without the use of a lens system, because all copies would be made on a one-to-one size basis.*[1012]

In 1961, Shoulders wrote extensively[2254] about using electron-beam-activated machining techniques to produce microelectronics components. The above passage clearly suggests that he envisioned such systems could ultimately be capable of self-replication. Shoulders appears to have been the first to discuss beam-based machine replication, a concept subsequently briefly explored by Taylor in 1978 (Section 3.10) and Freitas in 1981 (Section 3.14).

Four decades later, much progress has been made in this field, though as yet no replication has been achieved — although e-beam text-writing garnered Newman the second Feynman challenge prize in 1985 (Section 4.6). Electron beam induced deposition (EBID) is the process of using a high-intensity electron beam within an electron microscope to induce the formation of structures on the scanned surface.[2257,2270] EBID is a slow but versatile direct-write additive lithography process for the fabrication of mesoscale and nanoscale structures with high lateral accuracies. In this process, the microscope interior is filled with a low pressure precursor gas which is readily broken down under intensive e-beam illumination. For example,[2258] $W(CO)_6$ carbonyl gas[2259-2261] or WF_6 gas[2262] is used to grow tungsten carbide or tungsten wires, $Cr(CO)_6$ and $Re_2(CO)_{10}$ are used to grow chromium and rhenium nanorods,[2261] $Al(CH_3)_3$ is used to grow aluminum, $C_7H_7O_2F_6Au$ to grow gold, and (methylcyclopentadientyl)trimethylplatinum is used to grow platinum. In the EBID process, the electron beam is trained on a spot and held there, whereupon the precursor gas breaks down locally, depositing metal atoms only on the spot. As the beam continues to hit the spot, more atoms are deposited and a cylindrical column of metal grows, typically at a rate of ~3-300 nm/minute.[2263] By slowly translating the beam position in the XY plane and controlling the substrate angle and the growth conditions, 3-dimensional nanostructures such as atomic force microscopy tips,[2264,2265] interconnects,[2277,2278] walls,[2277] and more complex structures,[2266] including a world map printed on a spherical 60-micron resin microsphere with 10 nm features,[2267] have been made via "electron beam stereolithography." (See also Section 3.20.)

Koops notes that objects are readily constructed in vertically free-standing geometric shapes such as Y's, X's, and more complex structures containing internal voids such as arches or closed loops atop columns (i.e., round or square tennis-racquet shapes),[2268] including in one case a "three-dimensional build-up with conducting material resembling a field emission electron source, having an emitter tip and an extractor ring around it...[with] a capacitance of 24 aF between the tip and the ring" and in another case an artistic "Micro Coliseum" structure made by "FIB [focused ion beam] assisted deposition using a hydrocarbon precursor gas. The diameter of the structure is 1.8 μm, its height is 0.5 μm, the employed linewidth of the arches constructing the building is 0.08 μm." EBID has also been used to deposit carbonaceous structures,[2269-2274] ruthenium nanoparticle chains,[2275] and a variety of conducting and nonconducting materials.[2276-2279] Conductive nanostructured devices such as field emission sources have been fabricated[2280,2281] — single-atom STM tips can emit up to 10 microamp in field emission mode,[2282] although 0.1-1 microamp is more common for field emission from carbon atomic wires.[2283] Electron emission from EBID-grown columns or tips has been widely reported in the literature.[2284-2290]

EBID resolution is somewhat restricted[2291] because electrons scatter quickly in solids, beam electrons are mutually repulsive, and electron wavelengths are typically 20-50 nm. This often limits practical e-beam lithographic resolution to dimensions >10 nm, although resolutions as small as 2 nm have been obtained in a few materials,[2258] wires 80 nm in diameter have been fabricated with surface roughness below 2-3 nm,[2292,2268] tips for AFM/STM work can be made with radii of ~5 nm,[2270,2272] and EBID-fabricated carbon supertips have "customizable shapes with features down to below 10 nm".[2274] Unlike CVD (chemical vapor deposition), EBID is not a thermal decomposition process, so the purity of the deposit is often much lower unless the substrate is heated.[2280,2293] However, a few high-purity free-standing metal nanorods have been made by EBID,[2261] and a rapid fabrication process could be achieved by controlling the e-beam spot position with a computer, as demonstrated by Koops et al,[2280] or by employing multiple beams to achieve parallel operation.

Related opportunities for crude atomic or molecular positional assembly may exist with other emerging technologies, as, for example, the beam lithography/nanostencil technique under investigation by IBM Zurich in their "ATOMS" project,[2294] neutral molecular beam deposition,[2295] 3-D proton beam nanolithography,[2296] the manipulation of Bose-Einstein condensates along an "atomic conveyor belt" above a silicon chip,[2297] light-driven molecular assembly,[2298] atomic holography,[2299] and various proposals for quantum mechanical automata.[2300,2301] Older techniques of automated electrodeposition microfabrication[1122,1123] employ a fine-tipped probe in an electroplating solution to locally electrodeposit metals out of solution to form microstructures, such as regularly-spaced arrays of 100-nm tall nickel columns[1124] or >100-layer 3-D patterns using layers a few microns thick.[1123]

4.8 Laing Molecular Tapeworms (1974-1978)

Starting in 1974, Laing[557-563] proposed a hybrid cellular-kinematic machine replicator system which would compute and construct by means of a repertoire of simple mechanical actions (e.g., sliding local shifts of contact, local changes of state, and local detections of such state changes). The system would manipulate componentry of the same sort of which it is itself composed, and would in essence comprise a molecular tape that replicates, making more tapes identical to itself, using a universal Turing machine motif (Figure 4.28(A)). Machines of the system can imitate the actions of any Turing machine or of any robot system like themselves.[558] Notes Laing:[557] "We focus on artificial macromolecular machines. In form these macromolecular machines are chains (possibly folded and interconnected; Figure 4.28(B)) of basic molecule-like constituents....a molecular machine, an automaton device all of whose basic constituents and operations are the sort that reasonably may be said to be possible for biological systems at the macromolecular level....both machine and description will observe biological reasonableness."

The Laing kinematic automaton system is related to both the cellular automaton system and the projected kinematic machine system of von Neumann, as well as to the basic Turing machine concept.[557,559] In the Laing system, connected strings of finite state automaton componentry interact by making sliding contact and sending signals into each other. In this system, new components are recruited from the surrounding space at the ends of the interacting strings. These kinematic automata strings can be viewed as a mathematically precise analogy to certain biological processes at the macromolecular level and "might better be called molecular machines."

In one version[557] composed of rigid constituents (Figure 4.28(C)), Laing's kinematic replicating system consists of a program chain interacting with a tape chain. The tape chain is envisioned as a string of molecules of a sort able to take on two distinct physical states (e.g., 0 and 1), "which might in a physical molecule correspond to the presence or absence of an auxiliary molecule or to one or another of two distinct orientations of a molecule type." The program chain also can be represented in a string of effector molecules, and there are ten basic instruction types (requiring 10 different types of effector molecules): (1) write zero or "W(0)"; (2) write one or "W(1)"; (3) move left or "L"; (4) move right or "R"; (5) halt or "H"; (6) no operation or "NOP"; a branch instruction consisting of (7) an origination conditional transfer or "CT" molecule and (8) a destination transfer target or "TT" molecule; (9) a "detachment" molecule which when "activated and in temporary association with a molecule, will cause the severing of the structural attachment that molecule has with its predecessors"; and (10) a "synthesize" molecule which upon "being brought into active association with a passive molecule (a parts blank) will cause the passive molecule to change its state."

In the operation of the molecular machine, a string of program molecules is in sliding contact with a tape molecule string at a single location. If the active program molecule is a W(0), it will affect the contacted tape molecule to place it in state 0; if a W(1), to place the

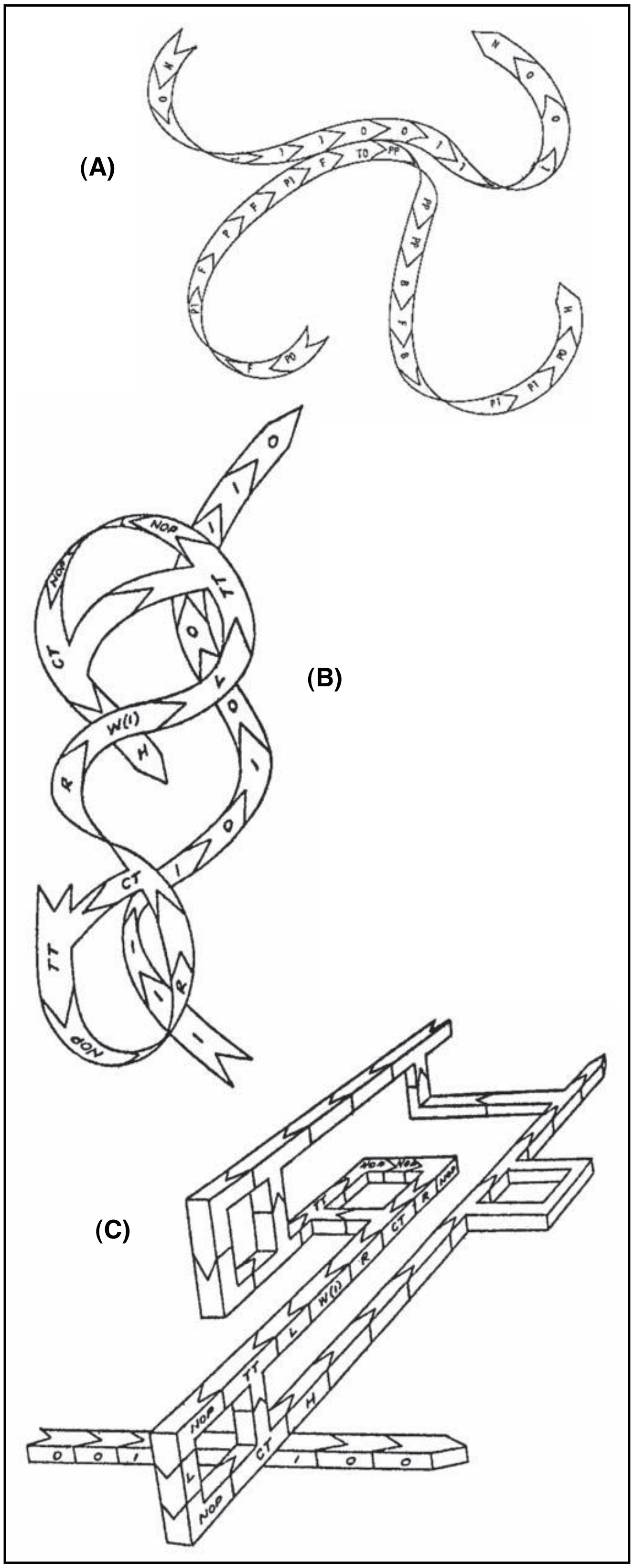


Figure 4.28. Laing molecular tapeworms.[557,560] (A) Turing machine in kinematic machine format — the lower string consists of program primitives which if activated will act on the passive "tape" primitives of which the upper string is composed. (B) Active interconnected program molecule and associated passive tape molecule. (C) Active program machine and passive tape machine composed of rigid constituents. (courtesy of Richard Laing)

tape molecule in state 1; if an R, to produce a slide to the next tape molecule to the right; and so forth. If an R or an L would result in disengaging the program and tape molecule chains, then a new "0" molecule must be synthesized or otherwise be recruited from the environment and attached to the end of the tape molecule string.

The molecular machine, composed of program chain and tape chain, then replicates as follows:[557] "First, the molecular machine produces a string of molecules which is a description of itself. Referring then to this description, the molecular machine determines one-by-one the type and constituent required, then retreats to the end of the description string and synthesizes the required constituent. By continued repetition of this process the molecular machine will finally end with a sequence of molecules, the first half of which is its description in '0' and '1' molecules, and the latter half of which is an exact copy of the molecular machine constituent primary sequence. The detachment molecule can now be employed to sever the connection between the description molecule and the new molecule machine constituent sequence. We shall also want to be able to communicate an 'active' status to a region of offspring molecular machines, else offspring would possess no autonomous self-reproducing properties. During construction, and upon release, the presence in the primary constituent sequence of structure-forming properties will by self-assembly impose the requisite three-dimensional form."

More recently, simpler versions of self-replicating molecular strands or strings (e.g., "typogenetics") have been introduced by Hofstadter[418] (as a formal way to describe operations on DNA strings) and further discussed by Kvasnicka and Pospichal,[2302,2303] Lynch,[2304] Morris,[2305] Snare,[2306] and Varetto.[1659,2307] Hutton[2308] has performed computational simulations of artificial replicators that inhabit a virtual soup and are subject to simulated laws of artificial chemistry; see also our discussion of the JohnnyVon simulations in Section 2.2.2. The interactions of computational objects forming a "Turing gas" in a form of "algorithmic chemistry" have been investigated by Fontana.[597-599] Hatakeyama and Nomoto[2309] have used a "movable finite automaton" model to simulate the synthesis of a copy strand of mRNA from a (stringlike) sequence of DNA. Ikegami and Hashimoto[564] have also described a network model of self-replication involving machines and description tapes.

Finally, futurist William Atkinson[2310] while skeptical of machine phase nanotechnology[208] nonetheless believes that molecular assemblers based on "nano cellular automata" could produce copies of themselves or other structures made of diamond and other materials, possibly using a more organic or nonmechanical process.

4.9 Drexler Molecular Assemblers (1981-1992)

In 1981, Drexler[197] described the utility of holding and positioning molecular parts, introducing the concept of mechanosynthesis: "By analogy with macroscopic devices, feasible molecular machines presumably include manipulators able to wield a variety of tools. Thermal vibrations in typical structures are a modest fraction of interatomic distances; thus, such tools can be positioned with atomic precision....these arguments indicate the feasibility of devices able to move molecular objects, position them with atomic precision, apply forces to them to effect a change, and inspect them to verify that the change has indeed been accomplished....synthesis can then involve highly reactive or even free radical intermediates, as well as the use of mechanical arms wielding molecular tools to strain and polarize existing bonds while new molecular groups are positioned and forced into place. This may be done at high or low temperature as desired. The class of structures that can be synthesized by such methods is clearly very large, and one may speculate that it includes most structures that might be of technological interest."

By 1985, Drexler was widely lecturing about "replicating assemblers"[2311] and, starting in 1986, Drexler[199,208,2910] proposed in greater detail the molecular assembler,* a device resembling an industrial robot which would be capable of holding and positioning reactive moieties in order to control the precise time and location at which chemical reactions take place.** This general approach would allow the construction of large atomically precise objects by a sequence of precisely controlled chemical reactions. Much like the ribosome in biology (Section 4.2), an assembler would build various classes of useful molecular structures following a sequence of instructions. During this process, the assembler would provide full three-dimensional positional and orientational control over each new molecular component (analogous to the individual amino acid in the ribosome model) that is being added to a growing complex molecular structure (analogous to the growing polypeptide in the ribosomal model). In one simple approach not mentioned by Drexler, a molecular assembler might be capable only of noncovalent assembly operations (Section 4.18), wherein nanoparts are fabricated by other means and then presented to the assembler, which then assembles the nanoparts into working nanomachines. Alternatively, a molecular assembler could be capable of forming any one of several different kinds of chemical bonds (e.g., by changing tool tips), not just a single kind such as the peptide bond that the ribosome makes. In bonding atoms or molecules to one another, the assembler would provide any needed energy through physical force — especially if the reaction happens not to be energetically favored — thus performing machine-phase chemical synthesis or mechanosynthesis as opposed to the traditional means of solution-phase chemical synthesis.

At its most basic level, the simplest possible nanoscale molecular assembler that is capable of self-replication may be composed of one or more nanoscale molecular manipulator mechanisms. For example, the hypothetical diamondoid telescoping molecular manipulator arm (Figure 4.29) described by Drexler[208] has about 4 million atoms excluding the base and control and power structures. Doubling the size to $\sim 10^7$ atoms to account for support structures gives a molecular weight of ~100 megadaltons and a total molecular volume of ~140,000 nm^3 per arm. The arm is 30 nm in diameter and 100 nm in length, and a careful count reveals that the design includes exactly 49 parts excluding the base. Designed for high strength and stiffness, this robot arm should be able to hold a molecular fragment stiffly enough to make it react with the chosen end of a carbon-carbon double bond, possibly with an error rate of only 10^{-15} according to Drexler's calculations.[208] The robot arm could then guide chemical reactions with high reliability at room temperature in vacuo, with little need for sensing the positions of the molecules with which it is working.[2313]

---

* *But not a "universal assembler": "Though assemblers will be powerful (and could even be directed to expand their own toolkits by assembling new tools), they will not be able to build everything that could exist" (Drexler[199] at page 246). The term "universal assembler" appears only in a section heading in Drexler's popular work* Engines of Creation[199] *but not in the text; the term appears nowhere in Drexler's major technical work,* Nanosystems.[208]

** *Explains physicist Mark Gubrud[2312] helpfully: "The assembler can be viewed as a kind of flexible, programmable catalyst. In fact, it is like an active catalyst, an enzyme. Like an enzyme, by bringing the reactant directly to the site, it creates an extremely high effective concentration of reactants. It can also constrain reaction pathways and select transition states. So synthetic routes that are not available in conventional chemistry may become available with assemblers, as they are, also, with enzymes and other catalysts." For example, the Merkle-Freitas assembler described in Section 4.11.3 can be regarded as a mechanical enzyme with the chemical formula* $C_{195,231,007}H_{8,677,806}Si_{30}Sn_{30}$ *that autocatalyzes the manufacture of its own structure in a very specialized environment.*

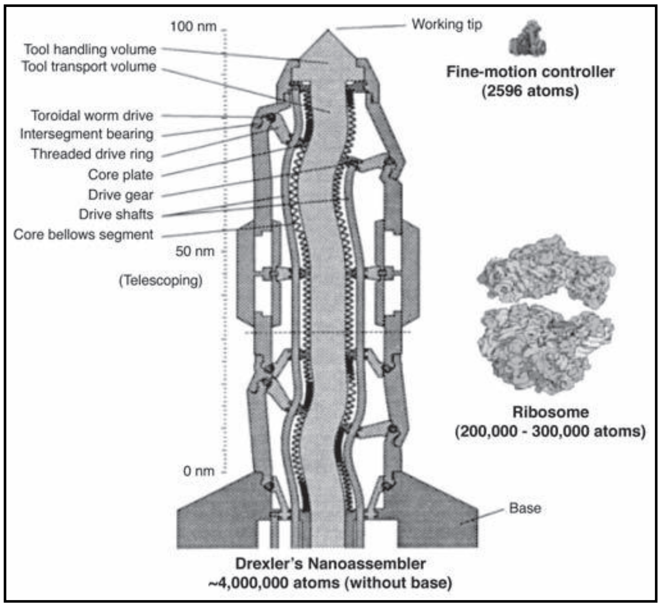


Figure 4.29. Cross-section of a stiff molecular manipulator arm, with identification of parts, courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html. Image of Fine Motion Controller © IMM, http://www.imm.org. Image of ribosome © PDB http://www.rcsb.org/pdb/newsletter/2000q4/mom.html.

Alternatively, using appropriate tool tips such an arm could grasp and manipulate individual prefabricated nanoparts in solution phase. Such assembly of nanoparts without fabrication might allow a much smaller tool set. The manipulator arm must be driven by a detailed sequence of control signals, just as the ribosome needs mRNA to guide its actions. Such detailed control signals can be provided by external acoustic, electrical, or chemical signals that are received by the robot arm via an onboard sensor or power transducer, using a simple "broadcast architecture",[208-210] a technique which can also be used to import power. Such transducers may be extremely small, on the order of $(\sim 10 \text{ nm})^3$ each.[208]

Drexler proposed the first generic design for a molecular assembler (Section 4.9.1) in 1986 in his popular book *Engines of Creation*,[199] published in 1986. In the early 1990s, following the dual approach laid out by the NASA Replicating Systems Concepts Team a decade earlier (Section 3.13.2), Drexler offered two distinct molecular manufacturing designs — a unit replication or "extruding tube" assembler model (Section 4.9.2) and a factory replication model (Section 4.9.3). In 1995, Drexler's Foresight Institute helped sponsor a special prize to be awarded to the first person or research group to build the first major components of a molecular assembler (Section 4.9.4). A fourth design of Drexler for a minimal assembler,[208] also published in 1992 in Drexler's technical book *Nanosystems*,[208] is described in Section 4.11.1.

4.9.1 Drexler Generic Assembler (1986)

In 1986, Drexler[199] described a generic molecular assembler as resembling a factory shrunk to a size smaller than an individual biological cell: "They will contain nanomachines mounted on a molecular framework and conveyor belts to move parts from machine to machine. Outside, they will have a set of assembler arms for building replicas of themselves, an atom or a section at a time. Imagine an advanced assembler that contains a million atoms: it can have as many as ten thousand moving parts, each containing an average of one hundred atoms — enough parts to make up a rather complex machine. In fact, the assembler itself looks like a box supporting a stubby robot arm a hundred atoms long. The box and arm contain devices that move the arm from position to position, and others that change the molecular tools at its tip.

"Behind the box sits a device that reads a tape and provides mechanical signals that trigger arm motions and tool changes. In front of the arm sits an unfinished structure. Conveyors bring molecules to the assembler system. Some supply energy to motors that drive the tape reader and arm, and others supply groups of atoms for assembly. Atom by atom (or group by group), the arm moves pieces into place as directed by the tape; chemical reactions bond them to the structure on contact. These assemblers will work fast. A fast enzyme, such as carbonic anhydrase or ketosteroid isomerase, can process almost a million molecules per second, even without conveyors and power-driven mechanisms to slap a new molecule into place as soon as an old one is released. A human arm can flap up and down several times per second, [but] an assembler arm will be about fifty million times shorter than a human arm, and so it will be able to move back and forth about fifty million times more rapidly. For an assembler arm to move a mere million times per second would be like a human arm moving about once per minute: sluggish."

"Assemblers will not replicate by themselves; they will need materials and energy, and instructions on how to use them. Ordinary chemicals can supply materials and energy, but nanomachinery must be available to process them. Bumpy polymer molecules can code information like a punched paper tape, but a reader must be available to translate the patterns of bumps into patterns of arm motion. Together, these parts form the essentials of a replicator: the tape supplies instructions for assembling a copy of the assembler, of the reader, of the other nanomachines, and of the tape itself.

"A reasonable design for this sort of replicator will likely include several assembler arms and several more arms to hold and move workpieces. Each of these arms will add another million atoms or so. The other parts — tape readers, chemical processors, and so forth — may also be as complicated as assemblers. Finally, a flexible replicator system will probably include a simple computer; this will add roughly 100 million atoms. Altogether, these parts will total less than 150 million atoms. Assume instead a total of one billion, to leave a wide margin for error. Ignore the added capability of the additional assembler arms, leaving a still wider margin. Working at one million atoms per second, the system will still copy itself in one thousand seconds, or a bit over fifteen minutes — about the time a bacterium takes to replicate under good conditions.

"Imagine such a replicator floating in a bottle of chemicals, making copies of itself. It builds one copy in one thousand seconds, thirty-six in ten hours. Each copy, though, will build yet more copies. Thus the first replicator assembles a copy in one thousand seconds, the two replicators then build two more in the next thousand seconds, the four build another four, and the eight build another eight. At the end of ten hours, there are not thirty-six new replicators, but over 68 billion. In less than a day, they would weigh a ton...."

4.9.2 Drexler Extruding Tube Assembler (1991)

In the "unit replication" or organismic model, the design most faithful to von Neumann's original kinematic concept, each replicator is an independent unit which employs the surrounding substrate to directly produce an identical copy of itself. Both the original and the copy remain fertile and may replicate again, thus exponentiating their numbers. Figure 4.30 shows the unit replicator design described informally by Drexler et al,[2910] taken from a Stanford University course (CS 404) that Drexler taught in the spring of 1988. Drexler's unit replicator design is a two-armed mechanical molecular assembler in an extruding tube architecture ~200 nm in diameter and ~650 nm in length, having a total molecular volume of ~20,000,000

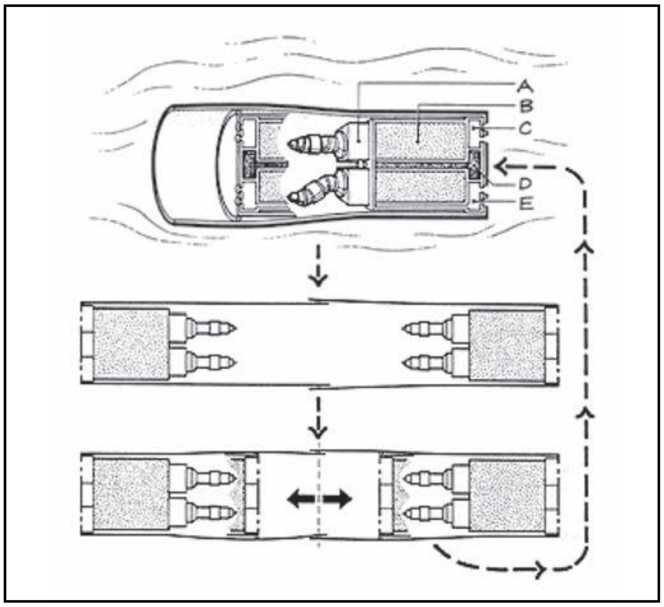


Figure 4.30. Drexler extruding tube assembler.[2910] (courtesy of K. Eric Drexler)

nm^3 (equivalent to a cube ~270 nm on an edge), containing ~1 billion atoms with a molecular weight of ~10 gigadaltons — very roughly the mass and scale of a very small bacterium (Section 5.3). For comparison, the average enzyme (a biochemical crimping tool) weighs perhaps ~0.1 megadalton, while a typical ribosome (a primitive "protein assembler") weighs 2.5-4.2 megadaltons (Section 4.2). Both parent and daughter machines are tubular in shape, and the daughter extrudes axially from the parent.

Drexler's unit replicator receives its control signals from an onboard nanocomputer,[208] which can accept stored instructions that are sequentially executed to direct the manipulator arm to place the correct moiety or nanopart in the desired position and orientation, thus giving precise control over the timing and locations of chemical reactions or assembly operations. Most of the interior of Drexler's device is taken up by a tape memory system that tells how to move the arm to build all the parts of the replicator, except the tape itself. The tape gets made by a special tape-copying machine. At the right-hand end of the replicator are pores for bringing in fuel and raw-material molecules, and machinery for processing them. The replicator would be able to build copies of itself when supplied with fuel and raw materials. In the middle are computer-controlled arms that do most of the actual construction. In Figure 4.30, (A) contains a nanocomputer, (B) a library of stored instructions, (C) contains machinery that takes in fuel and produces electric power, (D) is a motor, and (E) contains machinery that prepares raw materials for use. The lower diagrams illustrate various stages in a replication cycle, showing how the working space is kept isolated from the external liquid which provides the needed fuel and raw-material molecules.

The steps in the replication cycle — using a copy to block the tube, beginning a fresh copy, then releasing the old one — show one way that a machine could build a copy of itself while floating in a liquid, yet doing all of its construction work inside itself, in a better-controlled vacuum environment. Since the replicator contains about a billion atoms and each arm can handle about a million atoms per second, the whole construction cycle could be completed in less than 15 minutes. At that rate, one device can double and double again to make trillions in little more than ten hours. The replicators sit in a special chemical bath, absorbing what they need and making more replicators. Eventually, either the special chemicals run out or new chemicals are added to signal the replicator population to do something else. At that point, as suggested schematically by Figure 3.39, they can be reprogrammed for a production phase that will allow them to produce any other product that is within their physical capacity to manufacture, so long as it can be extruded from the front. These products may be long, and can unfold or be pieced together to make larger objects, so the small-bacterium size of the initial replicators need only be a temporary limitation.

Drexler[2910] notes that pure replicators of this sort "are useful as thought experiments to show how nanomachines can product more nanomachines, but specialized manufacturing equipment would be more efficient in practice."

4.9.3 Drexler Nanofactory Replication System (1991-1992)

In the "unit growth" or factory model, a population of specialist devices, each one individually incapable of self-replication, can collectively fabricate and assemble all necessary components comprising all specialist devices within the system, hence the factory is capable of expanding its size (or of manufacturing duplicate factory systems) indefinitely in an appropriate environment. In Figure 4.31, a molecular manipulator arm (Figure 4.29) performs molecular assembly operations on a passing workpiece attached to a conveyor belt. The workpieces eventually move from one manipulator arm to the next in series, each arm performing specialized tasks, finally resulting in a completed factory component which can be joined with other completed factory components, either to expand the size of the current factory or to replicate another copy of the original factory. Thousands of manipulator arms could fit in the volume of a single cubic micron.

As Drexler describes this approach in an early popular presentation[2910] in 1991: "This general-purpose assembler concept resembles, in essence, the factory robots of the 1980s. It is a computer-controlled mechanical arm that moves molecular tools according to a series of instructions. Each tool is like a single-shot stapler or rivet gun. It has a handle for the assembler to grab and comes loaded with a little bit of matter — a few atoms — which it attaches to the

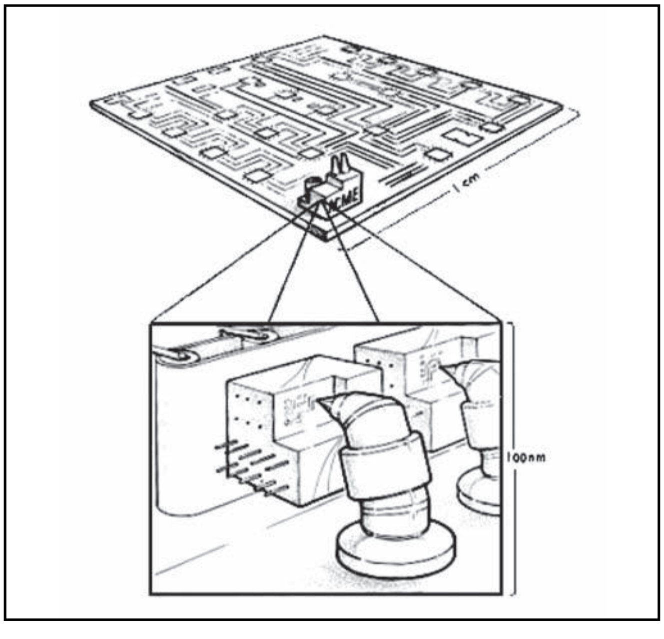


Figure 4.31. Drexler factory replicator.[2910] (courtesy of K. Eric Drexler)

workpiece by a chemical reaction. Molecular bonds hold things together. In strong, stable materials atoms are either bonded, or they aren't, with no possibilities in between. Assemblers work by making and breaking bonds, so each step either succeeds perfectly or fails completely. In [pre-molecular] manufacturing, parts were always made and put together with small inaccuracies. These could add up to wreck product quality. At the molecular scale, these problems vanish. Since each step is perfectly precise, little errors can't add up. The process either works, or it doesn't. Thermal vibrations can cause mistakes by causing parts to come together and form bonds in the wrong place. Thermal vibrations make floppy objects bend further than stiff ones, and so these assembler arms were designed to be thick and stubby to make them very stiff. Error rates can be kept to one in a trillion [10^{-12}], and so small products can be perfectly regular and perfectly identical. Large products can be almost perfect, having just a few atoms out of place."

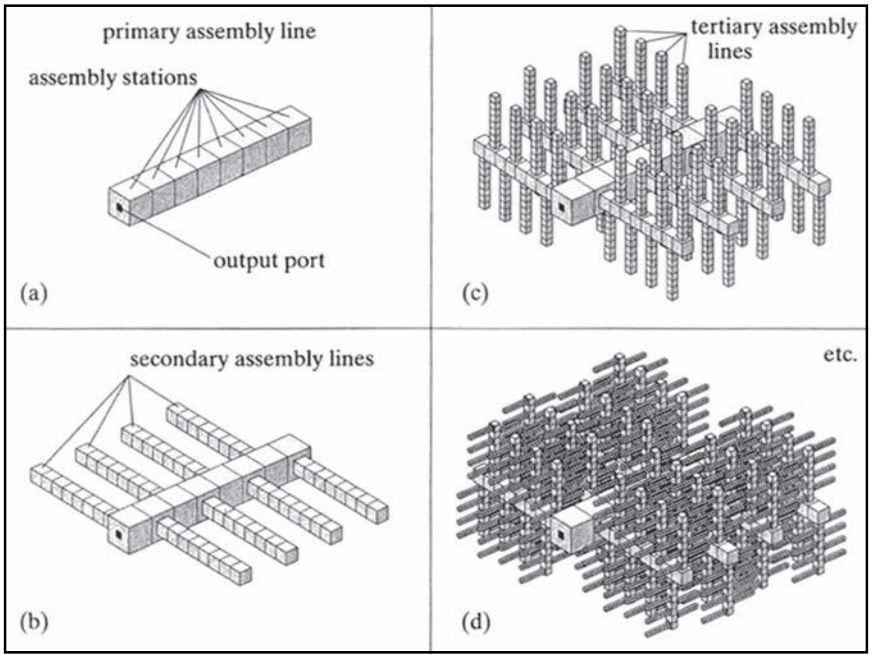


Figure 4.32. Drexler's exemplar architecture for convergent assembly. This simple model of a spatial arrangement for a hierarchical convergent assembly process[208] illustrates successively more detailed diagrams of the intended process. In (a), a primary assembly line consisting of a series of 8 assembly stations (drawn as cubes) performs the final 8 assembly operations in a hypothetical manufacturing process. In (b), 8 secondary assembly lines provide parts to the final lines. Panels (c) and (d) illustrate tertiary and quaternary assembly lines. Since each level of lines contains an equal volume, this pattern cannot be indefinitely extended without self-intersection; that is, the maximum radius of expansion is bounded. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

In a description of what a microscopic observer would see of this process, from inside a virtual reality simulation, Drexler writes:[2910] "One assembler arm is bent over with its tip pressed to a block on the conveyor belt. Walking closer, you see molecular assembly in action. The arm ends in a fist-sized knob with a few protruding marbles, like knuckles. Right now, two quivering marbles — atoms — are pressed into a small hollow in the block. As you watch, the two spheres shift, snapping into place in the block with a quick twitch of motion: a chemical reaction. The assembler arm just stands there, nearly motionless. The fist has lost two knuckles, and the block of nanocomputer is two atoms larger. [A few moments later], the assembler arm has moved by several atom-widths. Through the translucent sides of the arm you can see that the arm is full of mechanisms: twirling shafts, gears, and large, slowly turning rings that drive the rotation and extension of joints along the trunk. The whole system is a huge, articulated robot arm. The arm is big because the smallest parts are the size of marbles, and the machinery inside that makes it move and bend has many, many parts. Inside, another mechanism is at work: the arm now ends in a hole, and you can see the old, spent molecular tool being retracted through a tube down the middle. Within a few minutes, a new tool is on its way back up the tube. Eventually, it reaches the end. Shafts twirl, gears turn, and clamps lock the tool in position. Other shafts twirl, and the arm slowly leans up against the workpiece again at a new site. Finally, with a twitch of motion, more atoms jump across, and the block is again just a little bit bigger. The cycle begins again. This huge arm seems amazingly slow, but the standard simulation settings have shifted speeds by a factor of over 400 million. A few minutes of simulation time correspond to less than a millionth of a second of real time, so this stiff, sluggish arm is completing about a million operations per second."

The molecular manufacturing factory employs the principle of "convergent assembly"[208,213] to maximize efficiency. Using convergent assembly, molecular assemblers build blocks that go to block assemblers. The block assemblers build block assemblies, which go to system assemblers, which build systems, and so forth. "If a car were assembled by normal-sized robots from a thousand pieces, each piece having been assembled by smaller robots from a thousand smaller pieces, and so on, down and down," Drexler explains,[2910] "then only ten levels of assembly process would separate cars from molecules." In Drexler's proposed fractal convergent assembly process (Figure 4.32), the motion of components being assembled traces a tree in space. The trunk corresponds to the path traced by the final workpiece as the final components are assembled, the branches correspond to the paths traced by those components as they are assembled from simpler parts, and so forth — with the final stages resembling the middle and earlier stages, thus creating a fractal progression.[208] Merkle[213] has proposed a simpler configuration (Figure 4.33) that retains many of the desirable performance characteristics of Drexler's system. (See also Section 5.9.4.)

In his 1992 technical analysis of this factory approach to molecular manufacturing systems,[208] Drexler outlines an architecture for a system capable of manufacturing macroscopic product objects of mass ~1 kg and ~20 cm dimensions in a cycle time of ~1 hour, starting from a feedstock solution consisting of small organic molecules. The feedstock molecules enter the system through a molecular sorting and orientation mechanism (Figure 4.34), pass through several stages of convergent assembly using mill-style mechanisms (Figure 4.35), and then pass through several more stages of convergent assembly using manipulator-style mechanisms (Figure 4.29). The full system has 10 stages with progressively larger machines assembling progressively larger components at progressively lower frequencies (Table 4.1). If the manufacturing system can manufacture all of the components of which it is itself composed, Drexler's proposed desktop manufacturing system (system mass ~1 kg) would also be capable of self-replication in about 1 hour (Figure 4.33(D)).

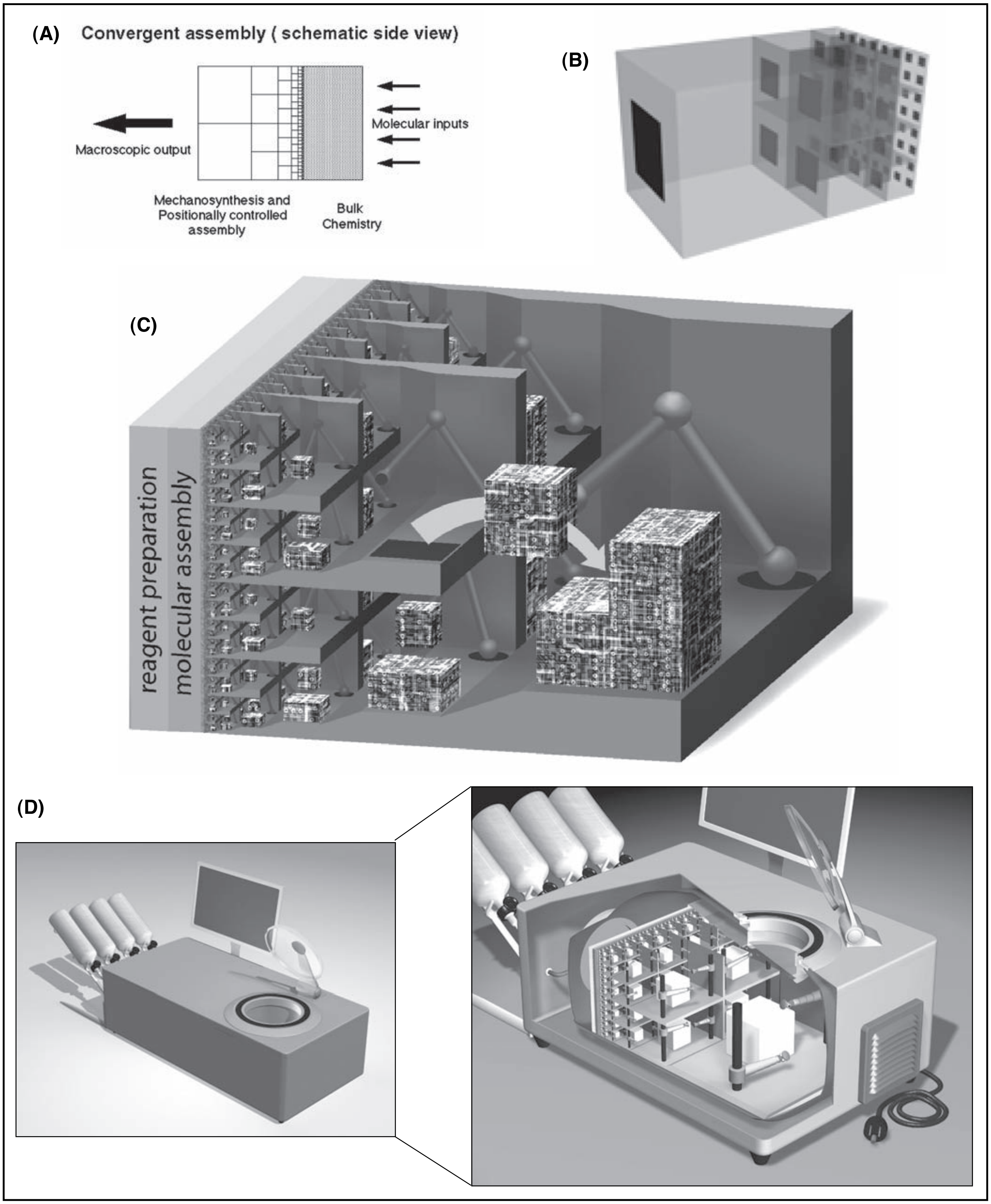


Figure 4.33. Merkle's exemplar architecture for convergent assembly used in Drexler's desktop molecular manufacturing appliance.[208] (A) Schematic side view of convergent assembly in which molecular inputs are combined in parallel into successively larger compound blocks, ultimately reaching the scale of macroscopic output. (B) Three stages of convergent assembly produce a final product of ~1 meter in size from 512 sub-sub-subassemblies each of which is ~0.125 meters in size (Section 5.9.4). (C) More detailed schematic side view of the convergent assembly of progressively larger compound blocks, ultimately reaching the scale of macroscopic output. Image courtesy of Eric Drexler, www.e-drexler.com. (D) External views of Drexler's proposed desktop molecular manufacturing appliance, outside view (left) and cutaway view of inner mechanisms (right). Images courtesy of John Burch, Lizard Fire Studios (3D Animation, Game Development) http://www.lizardfire.com.

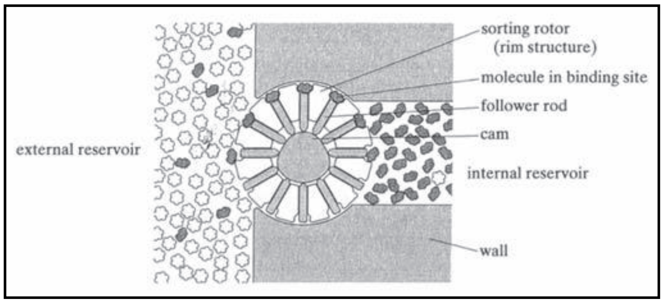


Figure 4.34. A molecular sorting rotor for the selective importation of molecular feedstock. In this sorting rotor based on modulated receptors,[208] a cam surface modulates the position of a set of radial rods. In the binding position (mapping the illustration onto a 12-hour clock dial), the rods form the bottom of a site adapted to bind molecules of the desired type. Between 10:00 and 2:00, the receptors undergo transport to the interior, driven by shaft power (coupling not shown). Between 2:00 and 4:00, the molecules are forcibly ejected by the rods, which are thrust outward by the cam surface. Between 4:00 and 8:00, the sites, now blocked and incapable of transporting molecules, undergo transport to the exterior. Between 8:00 and 10:00, the rods retract, regenerating an active receptor. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

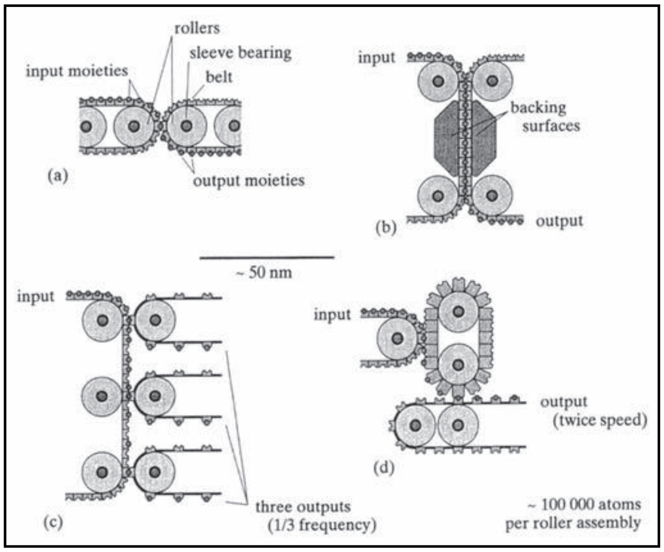


Figure 4.35. Schematic diagrams of mill-style reactive encounter mechanisms. These schematic diagrams show mill-style reactive encounter mechanisms for molecular assembly,[208] including mechanisms designed for: (a) simple contact and separation, (b) prolonged contact with opportunity for substantial cam-driven manipulation, (c) transformation of moiety transit frequency, and (d) transformation of moiety transit speed. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

Table 4.1. Drexler's exemplar molecular manufacturing system parameters (courtesy of K. Eric Drexler[208])

Level	Number of Sets	Number of Units per Set[a]	Number of Inputs per Product	Unit Operating Frequencies (Hz)	Product Scale (nm)	Mechanism Scale (nm)[b]	Unit Radiation-Sensitive Mass (fg)[c]	Total Mass of Mechanisms (kg)
Input ordering[d]	1	10^{17}	~1	10^{6}	0.5	20	0.02	0.002
Reagent prep.[e]	1	10^{17}	~1	10^{6}	0.5	20	0.06	0.006
Stage 1 mill[f]	10^{15}	100	100	$\leq 10^{6}$	1	20	0.60	0.06
Stage 2 mill	10^{13}	100	100	$\leq 10^{6}$	5	20	0.60	<0.01
Stage 3 mill[g]	10^{11}	100	100	$\leq 10^{6}$	20	100	0.50	<0.01
Stage 4 mill[h]	10^{9}	100	100	10^{4}	100	500	–	<0.001
Stage 5 mill	10^{6}	100	1000	10^{4}	1000	5000	–	<0.001
Stage 1 manip.[i]	10^{9}	2	10^{6}	500	10^{5}	2×10^{5}	–	<0.001
Stage 2 manip.	10^{4}	2	10^{5}	50	5×10^{6}	10^{7}	–	<0.001
Stage 3 manip.	1	2	10^{4}	5	10^{8}	2×10^{8}	–	0.020

a All numbers and frequencies are compatible with a ~1 gm/s throughput; within each stage, the combination of radiation-sensitive mass and number of units per redundant set is chosen to permit long operational lifetimes.

b Mechanism scale describes (e.g.) the size of a single rotor in a mechanosythetic device, not of a multi-mechanism unit.

c The radiation-sensitive masses of units of each kind are stated in femtograms (1 fg = 10^{-18} kg).

d The mass of the input-ordering subsystem is estimated from *Nanosystems*[208] Section 13.2.2.

e The mass of the reagent preparation subsystem is based on *Nanosystems*[208] Section 13.3.5.

f Stage 1, 2 mill units: the mass per encounter mechanism is assumed to be the same as in reagent preparation.

g Stage 3 mill units: the moving parts are assumed to be large enough to permit designs tolerant of radiation damage (Nanosystems[208] Section 14.2.2b), and the radiation-sensitive mass is that of product structures in transit through the unit.

h Stage 4, 5 mill units: the moving parts and product structures are assumed to be damage tolerant; the number of units per set is large chiefly to permit lower frequencies and speeds.

i Manipulator units: the arm structural mass is chosen to permit designs with stiffness >100 N/m, and with all bending-mode frequencies >100 times the unit operating frequency; the arm supporting structures are assumed to be 10 times more massive than the arms themselves.

Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

Drexler[208] summarizes as follows: "A wide range of macroscopic products can be made with good efficiency by using mills to make a diverse set of building blocks in the 10^{-7} to 10^{-6} m size range and then using manipulators to assemble them into macroscopic products. Inclusion of a secondary production capability that applies manipulators to smaller building blocks (at the moietal level where necessary) can provide unusual building blocks without requiring a dedicated mill mechanism. The exemplar system...makes the simplifying assumption of a hand-off from mills to manipulators at a single block size, 10^{-6} m [~1 micron]."

4.9.4 Feynman Grand Prize (Foresight Institute)

In an effort to stimulate scientific and engineering interest in constructing the first nanoassembler, in November 1995 the Foresight Institute (a not-for-profit organization founded by Drexler) created the $250,000 Feynman Grand Prize,[2314] with major funding contributed by Zyvex founder James R. von Ehr II and St. Louis venture capitalist Marc E. Arnold. The prize will be awarded to the individual or group that first achieves both of two significant nanotechnology breakthroughs — first, the design and construction of a functional nanometer-scale robotic arm, and second, the design and construction of a functional 8-bit adder computing nanodevice.

According to Grand Prize rules,[2314] the robotic nanomanipulator must fit entirely inside a 100-nm cube, carry out actions directed by input signals of specified types, be able to move to a directed sequence of positions anywhere within a 50-nm cube, complete all directed actions with a positioning accuracy of 0.1 nanometer or better, and perform at least 1,000 accurate, nanometer-scale positioning motions per second for at least 60 consecutive seconds. The adder must fit entirely within a 50-nm cube, and must be capable of adding accurately any pair of 8-bit binary numbers, discarding overflow, accepting input signals of specified types, and producing its output as a pattern of raised nanometer-scale bumps on an atomically precise and level surface. (J.S. Hall notes that a conventional 8-bit adder may be constructed using a total of 94 AND, OR, and NOT gates; using XOR gates, the total may be reduced to 37 gates.) Both devices may accept inputs from acoustic, electrical, optical, diffusive chemical, or mechanical means, although any mechanical driving mechanism used for input must be limited to a single linkage that either slides or rotates on a single axis. To demonstrate the capacity for mass-production, at least 32 copies of each device must be provided for analysis and destructive testing by judges. The device does not need to demonstrate self-replication to qualify for the Grand Prize.

4.10 Merkle Molecular Assemblers (1991-2000)

Following Drexler's original discussions,[199,208,2910] Merkle authored or co-authored a series of papers during 1991-1999 discussing various operational aspects and specific components of assembler design, including mechanosynthetic positional control,[219,221,2315] general design considerations for assemblers,[210-212] the broadcast architecture,[209] convergent assembly,[213] binding sites,[214] nanotech parts design,[2316,3050] positioning devices,[215,2017] mechanosynthetic path sets,[216] designs for a neon pump[2317] and a fine motion controller,[2318] and possible assembler casings.[217] Merkle explored four different specific architectures for molecular assemblers during the 1990s, including a generic assembler in 1992-1994 (Section 4.10.1), a replicating brick assembler in 1995-1997 (see Section 4.11.2), a convergent assembly factory system in 1996-1997 (see Section 5.9.4), and the cased hydrocarbon assembler in 1998-2000 (Section 4.10.2), described below.

4.10.1 Merkle Generic Assembler (1992-1994)

In 1992, Merkle published a set of broad specifications for a generic assembler design[211] which was to include positional mechanochemistry using "robot arms" similar to Drexler's telescoping manipulator (Figure 4.29), plus a physical barrier to keep the internal workings of the machine (in vacuum) separate from the external (liquid) environment. The list of required specifications was to include the following items: (1) the type and construction of the computer; (2) the type and construction of the positional device; (3) the set of chemical reactions that take place at the tip; (4) how compounds are transported to and from the tip, and how the compounds are modified (if at all) before reaching the tip; (5) the class of structures that the assembler can build; (6) the nature of the internal environment in which the assembler mechanisms operate; (7) the method of providing power; (8) the type of barrier used to prevent unwanted changes in the internal environment in the face of changes in the external environment; (9) the nature of the environment external to the device; (10) the transport mechanism that moves material across the barrier; (11) the transport mechanism used in the external environment; and (12) a receiver that allows the assembler to receive broadcast instructions.

The generic assembler was to be able to manufacture a range of diamondoid products, where "diamondoid" was construed to include "atoms other than carbon such as hydrogen, oxygen, nitrogen, sulfur, and other elements that form relatively strong covalent bonds with carbon." This would require, in turn, a significant number of different types of input molecules to be presented to the device as feedstock, in order to minimize the need for chemical processing: "To simplify the design, it might be desirable to provide all compounds in the feedstock in essentially the form in which they would actually be used. This would place the burden of synthesizing the specific compounds on whoever made the feedstock. If, on the other hand, we wished to provide only a relatively modest number of simple compounds in the feedstock, then there would have to be a corresponding increase in the complexity of the internal processing in the assembler in order to synthesize the required complex compounds from the simple compounds that were provided. Early designs will likely have limited synthetic capabilities and will be almost completely dependent on the feedstock for the needed compounds. As time goes by, some of the compounds provided in the feedstock will instead be synthesized directly within the assembler from simpler precursors. Ultimately, those compounds that can be synthesized more economically in bulk will not be synthesized internally by the assembler but will simply be provided in the feedstock. Those compounds which are more easily and economically made internally by the assembler will be eliminated from the feedstock." A multi-stage cascade approach (Figure 4.36) would be used to transport and purify input compounds,

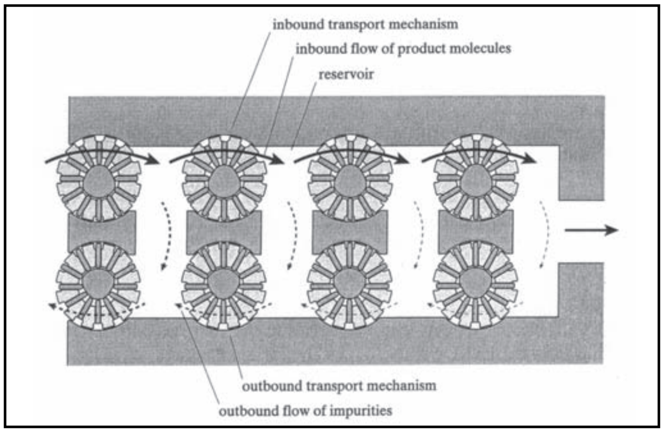

inbound transport mechanism
inbound flow of product molecules
reservoir
outbound transport mechanism
outbound flow of impurities

Figure 4.36. Schematic diagram of a staged cascade molecular sortation process, based on molecular sorting rotors. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

both because feedstock might contain impurities and because the many different feedstock compounds must be segregated before use.

The generic assembler was to include an onboard computer: "It might well be that electronic designs will provide the best performance, [but] a broad range of designs for mechanical computers exists [and] the components of the molecular mechanical computer could be made from the class of diamondoid structures." Additionally, the assembler was to include a mechanical pressure sensor to allow it to receive instructions acoustically through its liquid environment, which was regarded as a way to reduce onboard memory requirements: "Broadcasting instructions to the assemblers also means that the memory on board the assembler can be greatly reduced. Each assembler need only remember the small portion of the broadcast which pertains to its particular actions, and can ignore the rest. If the broadcast instructions are repeated periodically then each assembler need remember only enough instructions to keep it busy until the next broadcast is received. In the limit, each assembler could simply execute instructions intended for it as they were broadcast, and do nothing when instructions for other assemblers were being broadcast. This approach minimizes the memory that each assembler requires."

By the end of 1992,[210] Merkle had adopted the above limit of fully "stripped down" assemblers that would consist solely of a molecular constructor: "The computational element has been moved into a large, macroscopic computer where the computation is done once, and the simple instructions that result from the computation are broadcast to the actual constructors. The molecular constructors are thus 'gutless wonders' — they are barely able to receive and interpret some simple instruction, such as 'move your arm one nanometer to the left.' This architecture allows the molecular constructor to be simpler and smaller than a general-purpose assembler, while the computational device is a conventional macroscopic computer." Drexler's *Nanosystems*,[208] published earlier in 1992, had also proposed that "replacing computers and stored instructions with broadcast instructions can simplify molecular manufacturing systems."

Unlike later designs, Merkle's early generic design uses acoustic signals only to provide information, not energy, to the device. Merkle's generic assembler was to be powered by "chemical energy from fuel provided in the external environment."

4.10.2 Merkle Cased Hydrocarbon Assembler (1998-2000)

After abandoning his 1995-1997 "replicating brick" assembler design (see Section 4.11.2) because of several inconvenient features, in 1998 Merkle began work on a more technically detailed third assembler design[217] which he called a "cased hydrocarbon assembler." Reminiscent of peas-in-a-pod (Figure 4.37), Merkle's new design included an assembler device that floats in a solution feedstock and is completely enclosed within a flexible cylindrical graphene casing, allowing the gaseous interior environment to be kept separate from the liquid exterior environment. During a single replication cycle, the parent assembler device first inflates its casing, builds two copies of itself inside the casing, then ruptures the original casing (which is thrown away), pushing or releasing the two daughters out into the exterior environment. When fully unfurled, the assembler device is 200 nm in diameter and 1000 nm in length. The parent is destroyed during replication, but the assemblers increase their numbers during each replicative cycle and the number of daughters that each parent produces per generation can be made larger than two* to modestly improve replicative efficiency.

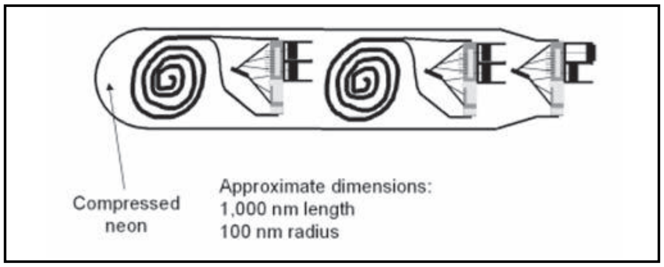


Figure 4.37. Schematic drawing of the Merkle cased hydrocarbon assembler.[217] Two HC assemblers have just been completed but not yet released. Their casings are shown rolled up, and the two pressure actuated pistons are shown as inactive (in the fully retracted position). The output of the demultiplexor is indicated, but the control lines from it have not been shown going to the various controlled components of the assembler to avoid confusion in the drawing.

Because evacuated single-walled carbon nanotubes with a radius exceeding ~2.7 nm are more stable when collapsed[2319] and because the graphene casing of Merkle's exemplar assembler is 100 nm in radius, it is necessary to pressurize the casing to prevent this collapse. Inert neon gas pressurized to 50-600 atm should be sufficient to inflate but not rupture the casing, but makes a near-liquid internal environment since the compressed neon will be 4-40% the density of liquid water according to van der Waals' equation.[228] During construction, the casings of inactive daughter devices are built rolled-up (like a sleeping bag). The volume of each rolled-up casing is 210,000 nm^3, or just 0.7% of the 0.031 micron^3 volume of the fully inflated casing — hence both daughter devices can easily fit inside the parent. The interior manufacturing systems are much the same as in the replicating brick proposal (Section 4.11.2), except that in the cased assembler proposal Merkle refers to "robot arm" manipulators and cites both Drexler's telescoping molecular manipulator arm and his own Stewart platform designs as examples, but without specifying which is to be used in this design.

Both control signals and mechanical power enter the device through two large ($\sim 10^4$ nm^3) externally-mounted pistons, rather than the few dozen internally-positioned pistons in Merkle's previous replicating brick design. This eliminates the need for pressure equilibration (between internal and external environment) evident in Merkle's replicating brick design — allowing high internal pressurization which prevents casing collapse — but adds a requirement for two new subsystems. First, a signal demultiplexor is needed to convert the force from two pistons into corresponding force on any one of several molecular control cables. Second, a system of interior cables to carry power and control signals is needed, which must be strung in a way which does not interfere with assembler operation. The cables are needed because in the cased assembler architecture, the source of power is physically separated from the manufacturing mechanisms, whereas in the replicating brick architecture the acoustic power is broadcast throughout the gas-filled interior of the device and thus is directly available to all interior mechanisms able to receive these signals. The cables are envisioned as a flexible rod inside a flexible sheath analogous to a bicycle derailleur cable, as for example a polyyne rod encased in a (9,0) carbon nanotube sheath. Pulling on the rod while pushing on the sheath produces a force that can be transmitted along the length of the cable.

** C. Phoenix[572] observes that the maximum efficiency of this replicative strategy cannot be significantly increased because the optimum number of daughters per generation appears to be approximately three. A complete quantitative discussion is in Section 5.9.2.*

The two pistons, each measuring 12 nm in radius and 20 nm in length, have different threshold actuation pressures. This allows either piston to be selectively addressed by adjusting the pressure of the feedstock solution. The pistons are operated at 10 MHz using a two-band signaling approach, one band for each piston. In this design, the lower pressure piston cycles the demultiplexor through its possible outputs (selecting which among the many output lines is to be driven), while the higher pressure piston drives the currently selected output, allowing the outputs of the demultiplexor to be selected and driven in any desired sequence using only two pistons. An operating pressure of 2 atm, with excursions to 1 atm to operate the low pressure piston and excursions to 3 atm to operate the high pressure piston, should suffice for reliable operation. The maximum pressure is significantly smaller than that proposed for the Drexler minimal assembler (Section 4.11.1) for two major reasons. First, by adopting a two-band signaling system (instead of Drexler's many-band signaling system) the number of pressure ranges that must be accommodated is reduced from many (perhaps 20 or more) to only two. Second, by reducing the number of pistons and locating them externally, their size and hence their sensitivity to pressure changes is increased. Fewer narrower pressure ranges reduces the maximum pressure that is required. The cased hydrocarbon assembler is composed of ~10^9 atoms. Assuming that on average the addition of one atom to an assembler will require 1000 pressure cycles, then a total of 10^{12} pressure cycles are needed to complete one replication cycle. At 10 MHz, this is ~28 hours.

Reviewing the rationale for his design efforts,[217] Merkle explained: "Today, we are unable to build *any* assembler. We are, therefore, searching among the space of simpler designs for systems which might be easier to make. The present design is not among the simplest because it is constrained by the requirement that it be able to fabricate stiff hydrocarbons. Designs that might be appropriate targets for direct synthesis with existing technologies are unlikely to be able to make diamond, but will probably work with molecular building blocks whose assembly is simpler and which impose fewer constraints on the environment. The present design is neither the next experimental target nor the final destination. It is a way point along the route from present capabilities to the future."

4.11 Extruding Brick Assemblers (1992-2003)

In all assembler designs which employ a physical barrier to maintain separate internal and external environments, the products of molecular manufacturing — including successive replicas of the manufacturing system itself — must eventually be delivered from the internal space to the exterior environment. At least three strategies to accomplish this are apparent. First, the export of product to the external environment can be allowed to permanently contaminate the interior environment of the assembler, whereupon the original assembler can no longer function and must be discarded. Second, product export can be allowed to contaminate the interior environment of the assembler, but the assembler is designed to reseal itself and remediate its internal environment post-export, after which remediation the original assembler can then resume manufacturing operations with some delay. Third, product export can be accomplished while continuously maintaining the integrity of the physical barrier during the export process — there is never any contamination of the interior environment of the assembler and the original assembler can resume manufacturing operations immediately following product export, with no delays. Examples of the third approach might include progressive airlocks, construction of internal partitions or sliding sealwalls to isolate the product object prior to export, discardable "shipping crates," or continuous extrusion systems.

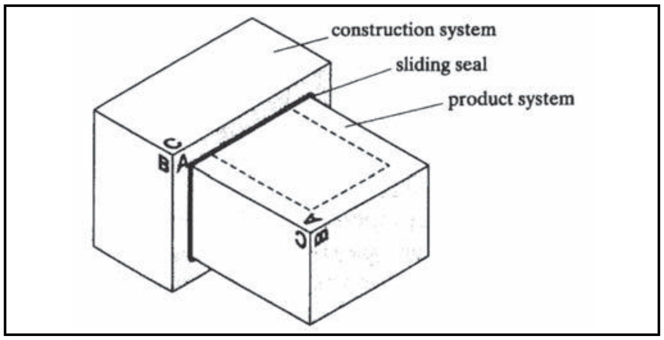


Figure 4.38. Schematic illustration of the extruding brick geometry for a molecular assembler. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission; http://www.zyvex.com/nanotech/nanosystems.html)

A simple example of the latter approach is the "replicating brick" or "extruding brick" geometry, first suggested by Merkle and described in Section 14.3.2 of *Nanosystems*[208] in 1992.* In this geometry (Figure 4.38), an exported object can have two physical dimensions as large as the two smallest dimensions of the manufacturing system, and can have a third dimension which is essentially unlimited. Thus delivered products can be of the same size or larger than the system that produced them, and just three replicative generations may suffice to increase all three physical dimensions of the original manufacturing system. (A more complex extrusion system could export product objects that are rolled up and later unfurl, as proposed by Merkle,[212] or that have nonrigid walls composed of the metamorphic surfaces proposed by Freitas in Section 5.3.2 of *Nanomedicine*,[228] allowing all three product dimensions to be simultaneously larger than those of the parent device because the product object can expand itself immediately after extrusion, like inflating a balloon.)

Three proposals for molecular assemblers employing the extruding brick architecture have been published in the literature — the Drexler minimal assembler (Section 4.11.1), the Merkle replicating brick assembler (Section 4.11.2), and the Merkle-Freitas molecular assembler (Section 4.11.3) — as summarized below.

4.11.1 Drexler Minimal Assembler (1992)

In 1992, Drexler (in *Nanosystems*,[208] Section 16.3) proposed a "minimal diamondoid-material mechanosynthetic system" explicitly specifying the extruding brick architecture (Figure 4.38). This device has "an inert [internal] workspace environment in which highly active reagent moieties can be positioned relative to workpieces with high precision and reliability." Drexler's minimal assembler would comprise ~100 moving parts and ~2×10^7 atoms, or ~160,000 nm^3 of diamondoid structures packaged into a total assembler volume of ~$(100\ nm)^3$. The mean error rate per manufacturing operation can be as poor as 10^{-8}, far less than the 10^{-15} error rate anticipated for more mature assembler systems.[208]

The assembler floats in a liquid solution consisting of feedstock molecules of several kinds, prepared by conventional chemical synthesis, "each having a reagent-precursor moiety at one end and a distinctive 'handle' of several dozen atoms at the other." Differences

---

** According to S.M. Krylov,[2320] a crudely similar architecture "was suggested for a self-replicating robot in the patent application submitted to USSR Patent Department in 1974 [see included figures]. Of course this robot was built from 'macro' parts, but the concurrence of conceptual solutions is obvious. By the way, it is clear that there are other possible shapes very close to replicating brick."*

between handles enable selective binding (e.g., as illustrated in Figure 4.34), whereupon: "Forces applied by a manipulator can drive the rotation of a receptor from the exterior to the interior of the enclosure, and can force the release of a bound feedstock molecule; the handle can then bind to a larger block with a standardized, grippable surface. A pair of manipulators (one can be an immobile gripper) can be situated so that their tips can interact. Bound feedstock molecules can then be moved, placed, and made to interact with flexible control of encounter sequence and geometry. The resulting mechanochemical transformations can generate a wide range of reagent moieties and subassemblies from a smaller range of feedstock molecules. In particular, relatively unreactive precursors (stable in solution) can be transformed into highly active reagents in the inert environment within the enclosure. Once prepared, reagents can be applied, transferring groups to (or abstracting atoms from) a workpiece.

Unfortunately, while operating, this assembler produces large amounts of garbage, necessitating a waste expulsion pump: "The preparation and application of reagent moieties will generate wastes in the form of discarded handle structures. These will typically have a volume greater than that of the product structure, and must be cleared from the workspace. The manipulator can deliver them to a relatively unselective positive-displacement pumping mechanism for expulsion into the surrounding solution. Spent handles might resemble feedstock molecules enough to compete for receptors. This problem can be avoided by either (1) ensuring that their use modifies structures important to binding, (2) ensuring that their concentration in solution remains very small, or (3) trapping them in an expandable external compartment (e.g., a bag)."

The internal "inert workspace environment" envisioned here is not vacuum, but rather "a helium-filled structure [that] can equalize interior and exterior pressures to minimize wall flexure. More precisely, an enclosure can include an expansion bellows, thereby concentrating flexure in a region designed to accept it. Evacuated regions would be needed (if at all) only inside actuators, and these could be pumped: the presence of a few molecules would be inconsequential. Helium can be admitted (and large molecules excluded) by helium-permeable pores. A suitable internal helium pressure will result if the surrounding liquid is in contact with gaseous helium, and if the mean fluid pressure does not vary too widely or too fast." Given a $\sim 10^6$ nm^3 interior volume and a mean gas mole-fraction impurity concentration $<10^{-9}$ in the helium gas, "the probability of the presence of a stray nonhelium molecule in any one device is <0.1, hence most [devices] lack any contamination. Many reactive contaminants would be neutralized by gettering, that is by providing sacrificial reactive surfaces with which they can combine without harmful effect. One such contaminant is hydrogen, the molecule most likely to enter through helium-permeable pores."

Control and power are delivered to the assembler acoustically. "Pressure-threshold actuators enable substantially independent control of several tens of mechanisms within a single manufacturing system; an indefinitely large number of identical systems can be driven through the same sequence of operations at the same time." Drexler describes two possible actuator systems: a high-pressure system with a 20,000 atm operating range and 20 distinct actuator classes using 5 nm^3 pistons having threshold actuation pressures in 1000-atm steps (i.e., 1000 atm for the first actuator, 2000 atm for the second actuator, etc.), and a low-pressure system with a 200 atm operating range and 20 distinct actuator classes using 500 nm^3 pistons having threshold actuation pressures in 10-atm steps (i.e., 10 atm, 20 atm, etc.). A drawback to this design is the problem of collateral actuation — as Drexler notes, "shifting the ambient pressure monotonically from the [threshold pressure] value for one class to that of another class, then back again, will cycle all actuators of intermediate [threshold pressures] exactly once." An ideal system would avoid this, allowing the control system to drive only the one desired actuator during each operation cycle.

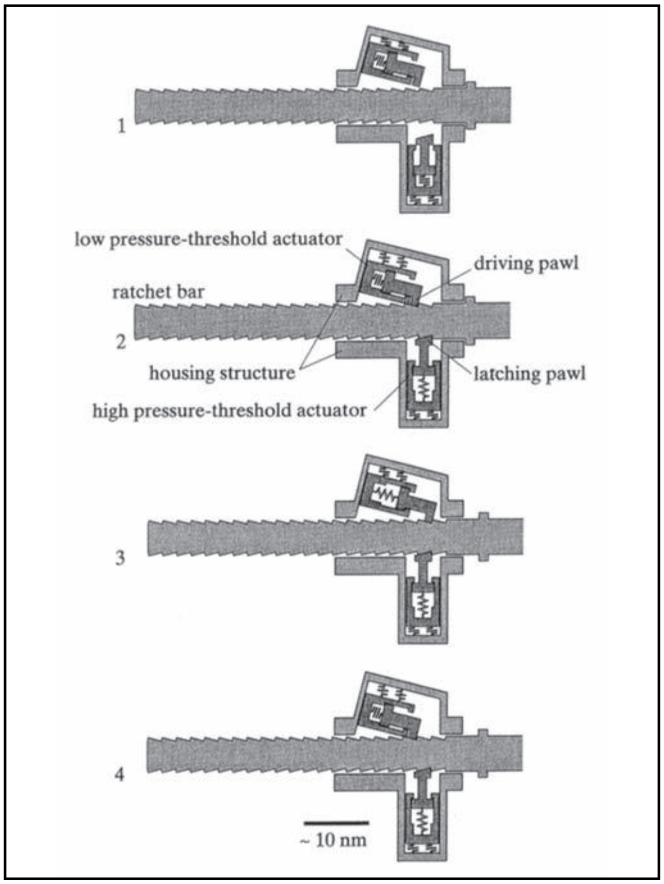


Figure 4.39. A ratchet mechanism driven by a pair of pressure-threshold actuators. Pressure-threshold actuators can drive a ratchet mechanism that moves a rod.[208] Engaging a latching pawl prevents the rod from moving left or right spontaneously, but the rod can readily be driven to the right by the following sequence of forces applied by the driving and latching pawls (which are mounted in the same housing structure): (1) At highest pressure, both pawls are retracted. (2) As the pressure falls, the latching pawl extends and engages, forcing the driving pawl to engage. (3) As the pressure drops through the active range of the driving pawl, it extends, forcing the rod to the right and momentarily lifting the latching pawl against the force of a spring; the latching pawl re-engages after moving one notch to the left. (4) An increase in pressure crossing the active range of the driving pawl resets it, preparing to move the rod a further step during the next downward pressure transition. A return to the highest pressure retracts both pawls again, allowing a bias force (not shown) to reset the rod position to the left. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

The arrival of acoustic control pulses from the external environment causes the assembler geometry to lengthen or shorten (via the "bellows" mechanism) with the shifting pressure, transmitting the pressure changes into the helium-filled interior of the device and thence to pressure-driven threshold actuators, which directly drive ratchet mechanisms (Figure 4.39) that extend or retract the struts of a Stewart platform-type manipulator (Figure 4.40); such manipulators are already well-known in commercial macroscale robotics.[2321]

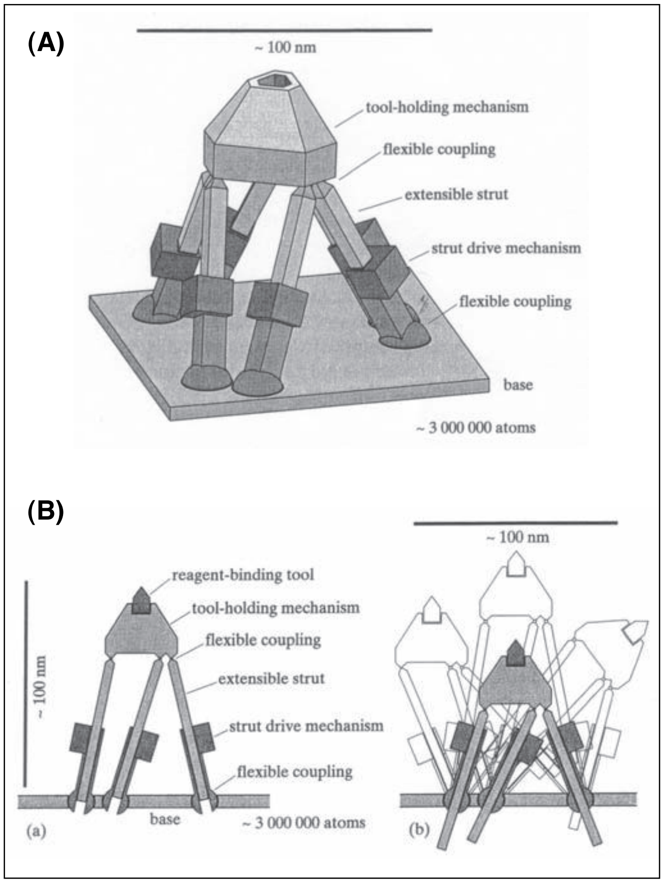


Figure 4.40. A positioning mechanism based on the Stewart platform. (A) This six-strut positioning mechanism has a joint at each end, shown for simplicity as ball-and-socket joints at the base and as flexible point attachments at the top. Each strut has a set of actuators able to adjust its length. (B) The figure at left shows a two-dimensional schematic of a Stewart platform based positioning mechanism, whose kinematics correspond to three of the six degrees of freedom of a full three-dimensional platform. The figure at right illustrates a portion of the available range of motion. Note that the lateral range exceeds the length of the arm in a retracted position. (courtesy of K. Eric Drexler.[208] Copyright © 1992 by John Wiley & Sons, Inc. Used with permission. http://www.zyvex.com/nanotech/nanosystems.html)

This manipulator then executes the physical motions necessary for all onboard manufacturing operations. "Using a manipulator mechanism able to reach a large portion of the interior space, complex behaviors can be implemented by complex control sequences, rather than by complex hardware. With 10 MHz actuator stepping rates, manufacturing can proceed at ~200 operations per second, enabling a system to build an object of its own complexity in about a day." However, no method is given by which a daughter device can be separated from the parent without disturbing the interior environment of the parent.

Drexler[208] makes the important additional observation that "a manipulator can replace many other control mechanisms. With a 'hand' in the workspace, various devices can be 'hand operated' — for example, a manipulator could push any one of a dozen levers to select and move a particular transport mechanism, or it could move a partially finished part from a clamp to a special jig for a series of operations, and then to its destination. To minimize parts and physical complexity, it may be desirable to use a manipulator for many purposes beyond the narrowly mechanochemical."

4.11.2 Merkle Replicating Brick Assembler (1995-1997)

During 1995-1997, Merkle[212]) adopted Drexler's minimal assembler proposal (Section 4.11.1) using the extruding brick architecture (Figure 4.38), and began to flesh it out. Merkle's device, which he called a "replicating brick" assembler, would be a sealed container with diamondoid walls floating in a liquid medium (Figure 4.41). It was noted that water or a suitable hydrocarbon such as hexane or other liquids would suffice, as long as they could dissolve all required feedstock molecules, as yet unspecified. The inside of the box would be compressed neon gas of unspecified pressure, which would allow acoustic power and control signals to be transmitted from the external liquid environment into the gaseous internal environment, and thence to pressure-driven threshold actuators each ~125 nm^3 in volume. A giant sliding end cap "piston" provides pressure equilibration between interior and exterior. A vacuum interior was explicitly rejected because of the requirement for "an internal medium that is able to carry acoustic (pressure) signals." Merkle agreed with Drexler that helium was an attractive alternative that should also work, but as the design might use sliding seals which should block diffusion of the inert gas, it is convenient to select the slightly larger-atom inert gas neon. "While sliding seals that block the passage of helium should be feasible, they must be tighter and present a greater design challenge." Also following Drexler, the broadcast architecture was explicitly adopted.

Merkle restricted his assembler "to the class of 'diamondoid' structures defined in *Nanosystems*[208] as including structures made from hydrogen; first row elements such as boron, carbon, nitrogen, oxygen and fluorine; and perhaps some second row elements such as silicon, phosphorous, sulfur and chlorine. Metals and other elements will generally (though not always) be excluded from consideration." However, Merkle had already recognized that the design might be further simplified, and anticipated his later cased hydrocarbon design, when he added: "We will frequently confine ourselves to hydrogen and carbon, as hydrocarbon structures are relatively easy to analyze and can often provide remarkable materials properties (e.g., diamond, graphite, and related structures). Potential energy functions which provide a good description of the behavior of hydrocarbons are available." Feedstock molecules would be transported from the exterior of the assembler to the interior using multiple stages of variable affinity binding sites. Once inside, molecular tools with highly reactive tips[2315] — including radicals, carbenes, and other highly reactive species of the general type found today in the CVD synthesis of diamond — would allow the synthesis of diamondoid structures. In 1997, Merkle[216] published a theoretical proposal for a partially complete mechanosynthetic tool set for building hydrocarbons.

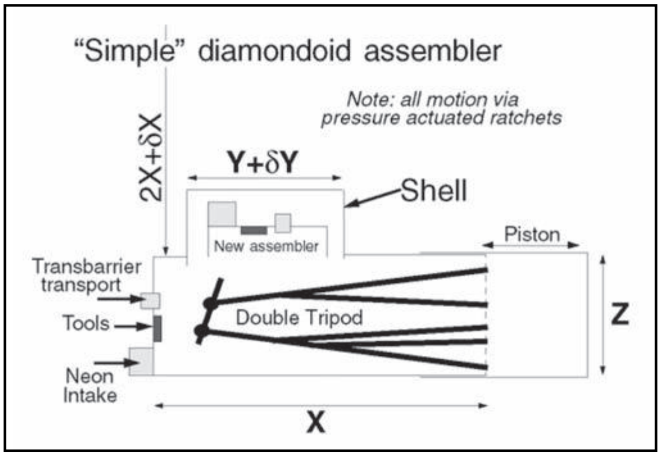


Figure 4.41. Merkle replicating brick assembler.[212]

Inside the assembler, an unusual double-tripod[215] Stewart platform — a relatively compact, six degrees of freedom positional device combining high stiffness with a wide range of motion — is used for the internal transport of molecular tools and other components via a simple "pick and place" procedure. This design simplification is possible because within the shell of the assembler, the location of every structural atom is known to within the positional uncertainty created by thermal noise — which is small in this case because the internal structural components have relatively high stiffness. Hence "the position of every structural atom in the system can be known to within a fraction of an atomic diameter with high reliability at room temperature and without the need for explicit positional sensing. This approach might be likened to a blind man assembling a product at a workbench where every tool and every component had a known position — the blind man would be able to perform the assembly operations despite the absence of positional sensing capabilities because the location of every nut and bolt was known."

As in Drexler's minimal assembler, Merkle's replicating brick employs some tens of pressure-actuated ratchets positioned as drivers directly on the struts of the manipulator device. But instead of Drexler's 20 different threshold pressure bands, Merkle usefully introduces for the first time a two-band signaling model: "Instead of addressing each individual ratchet by assigning it its own pressure range, we use pairs of ratchets and use only two pressure ranges. The first pressure range activates the first of the pair of ratchets, which we will call stepping ratchets, and causes a circular band to be stepped forward. At one or more points on the circular band are notches that indicate that the second of the pair of ratchets is to be made active. Each pair of ratchets has a unique set of notches in its associated circular stepping band. The second ratchets we will call working ratchets: they control the actual activities of the assembler. All working ratchets are either active or inactive, depending on the presence or absence of a notch in the stepping band. Signals sent in the second pressure range cause the active working ratchets to step but have no effect on the inactive working ratchets. By this method an indefinite number of working ratchets can be made active or inactive, and in fact can be made active and inactive in sets. The price we pay for this mechanism is the need to send stepper signals to activate the stepper ratchets and so select which working ratchets are to be active. While this will somewhat slow the signaling process, it has the distinct advantage over [Drexler's minimal assembler] that the addition of new working ratchets will not require an extension in the pressure range of the system. Thus, new working ratchets can be readily added late in the design or implementation cycle with minimal bother. In addition, the total pressure range that the system must accommodate is made much smaller, simplifying both the pressure control mechanisms and the design of the pressure actuated ratchets (the amount of overpressure that a ratchet is required to tolerate is greatly reduced, for example). Other devices required for assembler operation besides the struts of the double tripod will also be operated by threshold pressure actuated ratchets." One hidden complexity in this approach is the multitude of circular "stepping bands" at each control site which effectively act as a distributed multiplexor (Section 4.10.2) and could add significant bulk to the machine, and whose design is largely uncompleted.

While a selective transport mechanism for helium might only require simple pores large enough in diameter to permit the passage of helium but sufficiently small to exclude other contaminants, a selective transport mechanism for neon will be more complex because a pore large enough to allow neon to pass might also permit the entry of linear molecules composed of first row elements such as N_2, O_2, and CO_2. One mechanism for dealing with this problem would be to block both ends of a pore that is too short to hold any molecule longer than neon when the pore's ends are blocked, and then alternately open either end of the pore, making certain that both ends of the pore are never open at the same time as this would permit entry of linear molecules. Drexler[2317] has also proposed a molecular pump that molecular dynamics tests[223] suggest should be able to pump neon, but hydrogen and helium would likely be able to penetrate such a mechanism and hence should be excluded from the external liquid environment. Proposed designs for selective transport mechanisms "must be compared with the expected profile of contaminants in the surrounding liquid to insure that the rate of entry of contaminants is sufficiently small. While the concentration of helium should be kept small, some trace amounts of helium should be harmless. A few other small contaminants (such as N_2) might also be of concern. While it seems unlikely that they would enter as readily as Ne, H_2 or He, their entry rate might still be unacceptably high. If this proves to be the case, then their concentration in the external liquid environment must also be kept low. For the present proposal this is acceptable as a major objective is to simplify the design of the assembler even if that increases the cost of creating and maintaining the environment in which it operates. More generally, the complexity of the self-replicating component can often be reduced by imposing tighter constraints on the environment in which it functions."

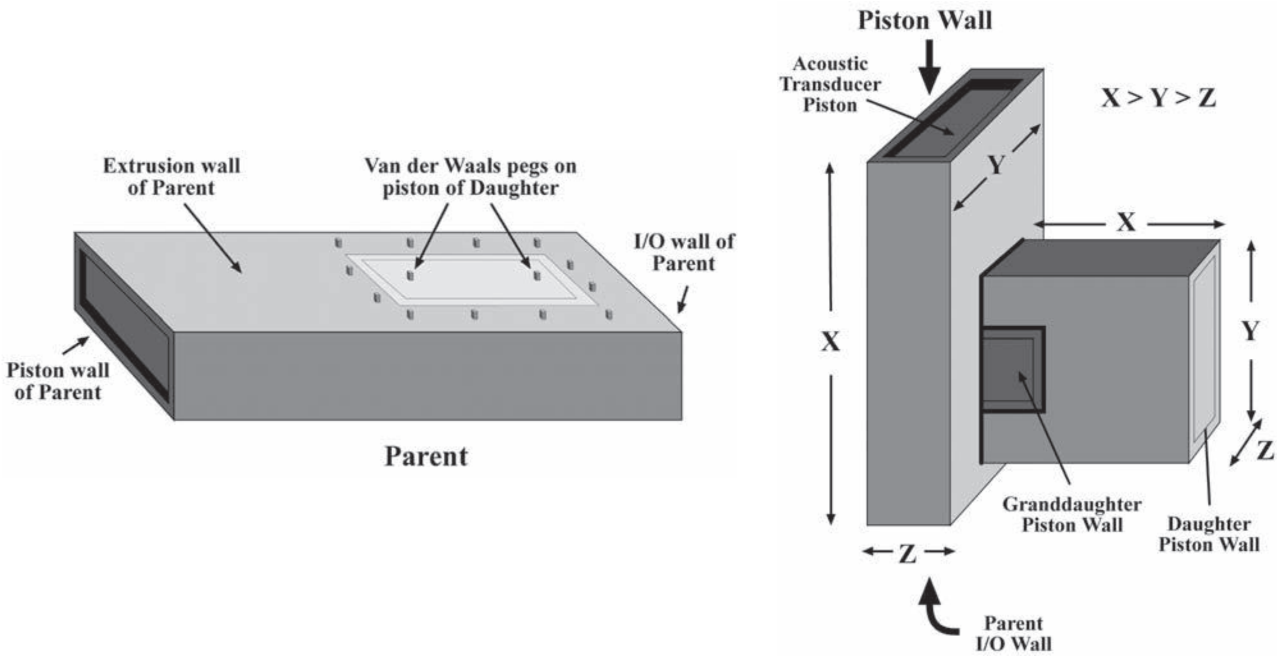
Merkle notes that self-replicating systems that employ a barrier to prevent external contaminants from entering the internal regions may also require a method of increasing the volume of the internal region, and that the replicating brick approach will allow this: "A brick with dimensions $X > Y > Z$ extrudes a new brick along the Z axis oriented such that the Y dimension of the newly extruded brick is aligned with the X dimension of the original brick, and the Z dimension of the newly extruded brick is aligned with the Y dimension of the original brick. The X dimension of the newly extruded brick is aligned with the Z dimension of the original brick, but because this is the direction of extrusion the fact that $X > Z$ does not create a problem."

Because it was unclear how to extrude a daughter without poisoning the interior environment of the parent, Merkle proposed extruding a "hollow shell" of more than twice the parental length, permitting "the construction inside it of two assemblers of dimensions X, Y and Z. When the two new assemblers have been manufactured inside the hollow shell, the shell is pushed out of the original assembler. This breaks the seal of the original assembler (the parent 'dies' in the process of releasing the two offspring) and opens up one end of the hollow shell, thus permitting the two newly manufactured assemblers to exit the shell. While this process is clearly wasteful (retaining the parent assembler in a functional state would be desirable), it simplifies the design of the extrusion process as the hollow shell is called upon to perform only a single task, rather than also acting as the wall of the new assemblers. Changes in the design of the hollow shell and its extrusion process have little impact on the design of the assembler." However, as with Merkle's later cased hydrocarbon design and even with Drexler's earlier minimal assembler design, a significant amount of waste material is generated and (in Merkle's designs) all replicative generations prior to the last are thrown away as garbage, an unfortunate result.

4.11.3 Merkle-Freitas Hydrocarbon Molecular Assembler (2000-2003)

A new design for a molecular assembler employing the extruding brick architecture, drawing upon modified elements of earlier designs (Sections 4.11.1 and 4.11.2) and introducing new design elements, resulted from a multi-year collaboration between Merkle and Freitas during 2000-2003. The Merkle-Freitas molecular assembler design repairs all known defects of earlier efforts and addresses additional problems not previously recognized by others. For example, the acoustic power/control piston count is reduced to one, allowing volumetric displacement, power input, efficiency, and reliability to be maximized. The proposed control signal demultiplexor is eliminated in favor of a much simpler control chain concept. The design is further simplified by the elimination of all gases from the interior (substituting a vacuum), by adding a novel "elevator" mechanism, and by eliminating all internal cabling which would be relatively difficult to assemble reliably. The continuous extrusion of daughters is achieved while maintaining full external seal integrity of parental device walls, thus preventing the destruction of parental devices following replication. All waste products — including molecular effluents (e.g., spent parts handles, gases), ruptured casings, and destroyed parental devices — are eliminated, yielding a 100% clean, environment-friendly, zero-waste molecular manufacturing system, the first such ever to be proposed.

A summary description of the Merkle-Freitas hydrocarbon molecular assembler design appears below. A more complete description of the design with all available details may be published elsewhere at a future date. (A few details are in Appendix B.)



Internal Dimensions (XYZ):	**323.572 nm x 80.00 nm x 40.00 nm**
Internal Volume:	**1,035,430.40 nm^3**
External Dimensions (XYZ):	**333.572 nm x 100.00 nm x 60.00 nm**
External Volume:	**2,001,432.00 nm^3** **(~2 mm^3 per trillion devices)**
Initial Mass:	**0.00390826 pg per device**
Initial Atom Count:	**203,908,873 atoms per device**
Initial Molecular Formula:	$C_{195,231,007}H_{8,677,806}Si_{30}Sn_{30}$
Carbon Feedstock Molecule:	**C_2H_2 (acetylene)**
Carbon Feedstock Solvent:	**n-C_8H_{18} (n-octane)**
Waste Byproduct:	**n-C_8H_{18} (n-octane)**
Highest Value Assembled Products:	**molecularly precise diamond and other rigid hydrocarbon structures**
Replication Time:	**10^6 seconds (~12 days)**
Power Demand, Single-Band Operation:	**14.2 pW (1-2 atm, 2-3 atm)**
Power Demand, Double-Band Operation:	**56.8 pW (1-3 atm)**
Acoustic Driver Frequency:	**10 MHz**
Instructions per Product Object Atom:	**50,000 bits/atom of product**
Placement Energy per Atom:	**0.073-0.291 pJ/atom C**
Manufacturing Production Rate:	**1 mg/sec per kg of devices**
Energy Cost of Manufacturing:	**$100,000/kg of product**
Manufacturing Defect Rate:	**<10^{-10} per atom of product**

Figure 4.42. Physical device specifications for the Merkle-Freitas hydrocarbon molecular assembler

4.11.3.1 Summary Description

The Merkle-Freitas Hydrocarbon Molecular Assembler (Figure 4.42) would be an entry-level molecular manufacturing device which allows the unitary fabrication and extrusion of molecularly precise rigid hydrocarbon product objects, including objects like itself. The Merkle-Freitas assembler is a "minimal assembler" design that requires a minimum of onboard structural complexity so that initial assembler devices can be constructed using the more limited tools and techniques available in a pre-assembler technology environment. Subsequent assembler devices can be conveniently built by the initial assembler device.

The Merkle-Freitas assembler floats in a 2 μm^3 liquid-filled room-temperature microfluidic reaction chamber containing n-octane hydrocarbon solvent in which acetylene feedstock molecules are dissolved. Acetylene molecules are mechanically transported into the device and employed as a source of carbon to construct a product object which is slowly extruded from the device, then released from the device upon completion of manufacture. Solvent molecules of n-octane are also mechanosynthesized and exported as a harmless byproduct to carry off excess hydrogen safely, resulting in a zero-pollution manufacturing system. A pair of 7-strut Stewart platform manipulators mechanically operate the feedstock molecule import and byproduct molecule export mechanisms, and also manipulate an onboard mechanosynthetic tool set[1,2322-2325] to build (1) diamond or other stiff hydrocarbon product objects to molecular precision, and (2) byproduct molecules. The manipulators receive power and step-by-step product/byproduct manufacturing instructions as a series of external pressure pulses broadcast at 10 MHz throughout the solvent fluid. These pulses originate from an acoustic signal generator abutting the microfluidic reaction chamber, and subsequently are transduced by an onboard piston into linear actuation motions which in turn drive manipulator motions coupled through a mechanical control chain system. Tight sliding seals maintain internal vacuum at all times.

4.11.3.2 Product Object Extrusion

The Merkle-Freitas Hydrocarbon Molecular Assembler includes an interior space and an exterior space, separated by a barrier consisting of a piston attached to an elevator plate. The interior space is a controlled environment where various delicate operations can be performed. The exterior space is a less-controlled environment which provides feedstock and physical support. All manufacturing takes place on the inside, in the controlled vacuum environment. The Merkle-Freitas assembler employs an "extruding brick" architecture which permits the manufacture of objects — whether valuable product or additional assemblers — of sizes smaller than, equal to, or larger than the original manufacturing system, enabling easy scalability. During a replication cycle (Figure 4.43), the parent device extrudes the daughter device, after which both parent and daughter may extrude a subsequent generation, and so on.

Geometrically, the Merkle-Freitas assembler is essentially a rectangular box. The four large external sidewalls of the daughter device are smooth and parallel as they are extruded. During replication, the four sidewalls establish a tight seal with the inside edges of a rectangular extrusion hole located in the extrusion wall (one of the two largest of the four sidewalls) of the parent.

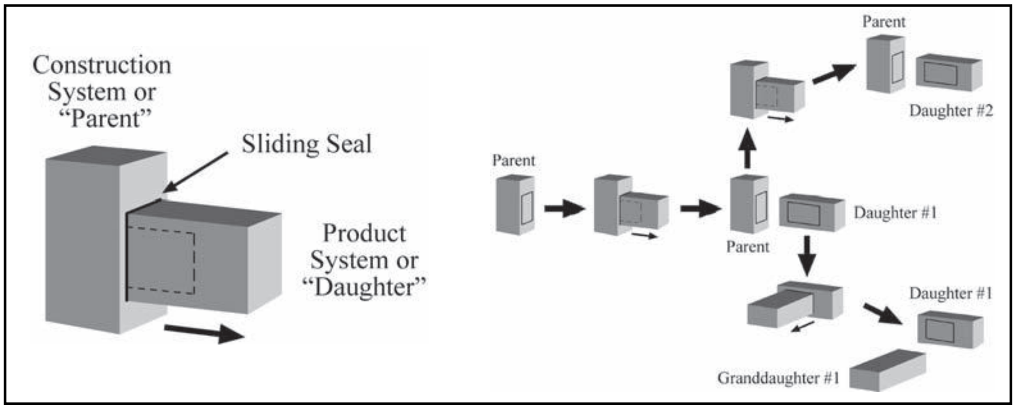
Initially, the extrusion hole of the parent is plugged with the premanufactured piston end wall (the small YZ face containing the piston that emerges first) of the future daughter. As the daughter is manufactured and extruded, the extrusion hole of the daughter is plugged with the premanufactured piston end wall of the future granddaughter, thus maintaining vacuum inside both parent and daughter.

Each piston end wall lies flush with the sidewall in which it is embedded. When replication resumes, the parent extrudes its daughter with the piston end wall of the future granddaughter already installed in the daughter. The piston end wall of the granddaughter, along with the daughter's four sidewalls, slide in contact with the extrusion hole of the parent while the daughter is being extruded from the parent. Thus five of the six external walls of the device are smooth as they are extruded during the replication cycle. Once a section of the daughter is clear of the parental extrusion hole, this surface smoothness may be modified as required (e.g., pop-out of spring-loaded van der Waals pegs; Section 4.11.3.4(11)). Additionally, after self-replication or extrusion of an improved device, some or all of these smooth walls could in principle be discarded, exposing whatever complex surface might be desired on any face. Similar considerations apply to the extrusion of desired non-self product objects during the analogous product manufacturing cycle.

4.11.3.3 The Broadcast Architecture for Control

Von Neumann's proposed architectures for self-replication,[3] the replicating lunar factory designs proposed for NASA[2] in 1980 by Freitas and by von Tiesenhausen and Darbro, Drexler's original assembler proposal in 1986,[199,208] and living systems all carry a complete set of plans for the system onboard the replicating system, in some form of internal memory. This is not a logical necessity in general manufacturing systems, as was observed by the 1980 NASA study (Freitas and Gilbreath,[2] p. 215): "It is quite possible to imagine the lunar factory operating nonautonomously...the in situ computer used simply as a teleoperation-management system for operations controlled directly by Earth-based workers [with] information necessary to accomplish [replication] supplied from outside. An alternative would permit the on-site computer to handle mundane tasks and normal functions with humans retaining a higher-level supervisory role."

Figure 4.43. Replication cycle of Merkle-Freitas assembler



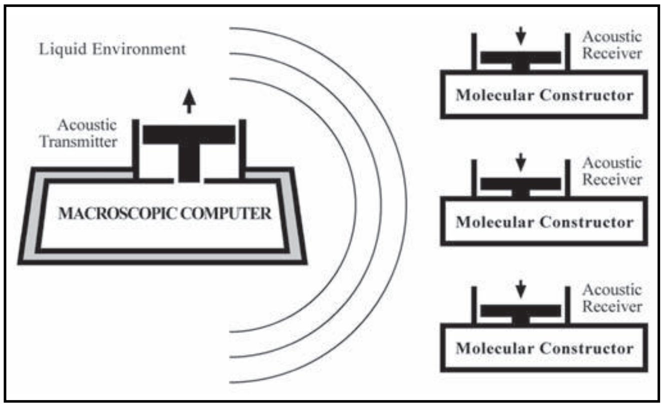


Figure 4.44. Schematic of the broadcast architecture for control.

Broadcast instructions (teleoperation) can enable system replication without internally stored instructions (Section 2.3.6), an arrangement which has been termed the “broadcast architecture”,[208-210] first described in the parallel-operation nanotechnological context in Section 16.3.2(a) of *Nanosystems*:[208] “Broadcast instructions. Replacing computers and stored instructions with broadcast instructions can simplify molecular manufacturing systems. Signals can be broadcast to molecular mechanical systems in several ways, but signaling by modulated pressure via mechanical transducers is both simple and adequate.” Similar conclusions have been reached by space technologists who suggest using remote-control procedures (e.g., “teleoperation,” “telepresence,” “telerobotics,” or “teleautonomy”;[18] see also Section 3.9) to reduce the high cost of items that would otherwise have to be expensively raised into orbit.

If we separate the “constructor” from the “computer” and allow many individual constructors to receive broadcast instructions from a single central computer, then each constructor need not remember the plans for what it is going to construct.[209] Rather, it can simply be told what to do as it does it (Figure 4.44). This approach eliminates the requirement for an integral repository of plans within the constructor (which is now the only component that must replicate) and also eliminates almost all of the mechanisms involved in decoding and interpreting those plans. This general approach is similar to the SIMD architecture of the Connection Machine,[2326] in which a single complex central processor broadcasts instructions to a large number of very simple processors. Storing the program, decoding instructions, and other common activities are the responsibility of the single central processor; while the large number of small processors need only interpret a small set of very simple instructions, thus allowing those small processors to retain comparatively simple structure and function. It is interesting that the living cell also employs the broadcast architecture[209] on a massively-parallel scale, using chemical rather than electrical or acoustic signaling: the DNA-containing nucleus acts as a central computer and data repository that broadcasts chemical instructions in the form of mRNA messenger molecules to up to ten million[228] structurally simpler manufacturing devices distributed throughout the eukaryotic cytoplasm, called ribosomes. Following the instructions received from the messenger molecules, the ribosomes manufacture all cytoplasmic proteins using unidimensional positional assembly (Section 4.2).

The specific advantages of the broadcast architecture are that: (1) it reduces the size and complexity of the self-replicating component, (2) it allows the self-replicating component to be rapidly redirected to build something novel, and (3) it is “inherently safe” (Section 5.11) because the individual constructors lack any capability to function autonomously, a feature that is particularly clear when the central computer is macroscopic and under our direct control. For these reasons we explicitly adopt the broadcast architecture for control in our proposed design for a molecular assembler.

4.11.3.4 Hydrocarbon Assembler Subsystems

The Merkle-Freitas Hydrocarbon Molecular Assembler consists of 12 major subsystems, as illustrated schematically in Figure 4.45, quantified in Table 4.2, and summarized below:

1. **Acetylene Binding Site and Import Mechanism.** The acetylene binding site consists of a (9,0) carbon nanotube of open inside diameter 0.7 nm and 2 nm in length, long enough to contain up to 4 molecules of acetylene. The binding site is embedded in a diamond block drawer that can be mechanically slid back and forth through a rectangular hole in the I/O (input-output) wall of the hull while maintaining a tight seal. Once conveyed inside, an acetylene molecule is forced into the receiving chamber by a polyyne rod inserted into the binding site. A di-silicon radical (or other group IV element, possibly Sn[2322] or Ge;[2325] further modeling work is required to validate a specific molecular tool) aligned to the acetylene molecule inside the receiving chamber binds the acetylene covalently, whereupon the captured feedstock molecule can be safely transported elsewhere inside the device for further mechanosynthetic processing.
2. **Vitamin Binding Site and Import Mechanism.** When product objects consisting entirely of carbon and hydrogen atoms are to be fabricated, no vitamin imports are required during the manufacturing cycle. However, during the fabrication of a daughter device (e.g., self-replication) it is necessary to import 30 atoms each of Si and Sn (or other group IV element) so that the mechanosynthetic tool tips of the daughter may be constructed by the assembler. Chemically inert vitamin molecules consisting of an easily disassembled Si- and Sn-containing hydrocarbon complex are added at a parts-per-billion trace concentration to the external solvent fluid, but only a dozen of these molecules need be imported during the entire 10^6-sec replication cycle of the device.
3. **Octane Assembly Site and Export Mechanism.** n-Octane molecules are mechanosynthesized by combining excess hydrogen atoms with acetylenic precursors in a narrow hydrogen-passivated reaction bay that opens to the external solvent through an exhaust tube (terminating at the I/O wall) just beyond a narrow throat. After final synthesis and release of the n-octane molecule, a carbene rod is inserted into the bay and irreversibly forces the n-octane molecule through the resistive energy barrier at the throat and into the exhaust tube.

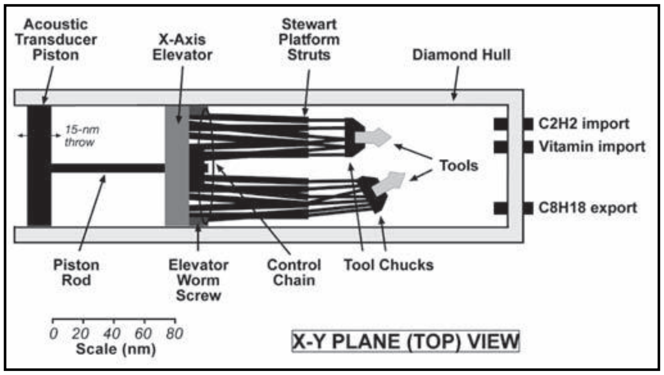


Figure 4.45. Schematic view of Merkle-Freitas assembler subsystems.

Table 4.2. Atom count and volume of all major subsystems in proposed molecular assembler

Assembler Sub-System (# in M.A.)	Atom Counts					Total Volume (nm^3)
	C	H	Si	Sn	Total Atoms	
Hull and Piston (1)	180,576,282	6,619,130	0	0	187,195,412	1,026,001.6
Elevator (1)	5,632,000	276,320	0	0	5,908,320	32,000.0
Daughter Downhang	4,928,000	464,720	0	0	5,392,720	28,000.0
Stewart Platforms (2)	2,804,751	736,535	0	0	3,541,286	15,936.1
Extrusion Springs	528,000	326,560	0	0	854,560	3,000.0
Piston Rod (1)	225,280	41,197	0	0	266,477	1,280.0
Control Chain (1)	140,800	105,504	0	0	246,304	800.0
Material Transport (3)	152,064	45,216	0	0	197,280	864.0
Elevator Screws (4)	138,230	17,408	0	0	155,638	196.3
Tool Tips (30)	105,600	45,216	30	30	150,876	600.0
Internal Vacuum	0	0	0	0	0	892,754.0
TOTALS	**195,231,007**	**8,677,806**	**30**	**30**	**203,908,873**	**2,001,432.0**

4. **Acoustic Transducer.** Externally generated pressure pulses between 1-3 atm drive the acoustic transducer through a 15 nm throw, producing a linear rod motion that provides information and mechanical power to the assembler device. The transducer has 3 components: (A) a piston plate (a hydrogen-terminated 10-nm thick rectangular diamond block with 45°-clipped corners to accommodate the legs of the van der Waals cage; see (11) below); (B) a piston rod 4-nm thick attached to the center of the piston plate and extending back through the elevator plate to engage the control chain mechanism that is attached to the other side of the elevator plate, in the assembler interior; and (C) the piston spring, attached to the exterior face of the elevator plate at one end and to the piston rod at the other end, to provide a restoring force. During replication, the daughter device is manufactured with its piston mechanically locked; slowly cycling through 4 atm unlocks this piston, synchronizing daughter(s) and parent (whose piston is already unlocked) in preparation for the next replicative cycle.
5. **X-Axis Elevator.** The 10-nm thick diamond elevator block permits motion of the entire piston-manipulator assembly along the X-axis of the assembler. Movement of the elevator is achieved by four capstan-driven worm screws that engage a linear sequence of shallow slots on the inner face of the hull wall. The control chain mechanism and Stewart platform struts are attached to the interior face of the elevator plate.
6. **Stewart Platform Manipulators.** All mechanical manipulations in the interior of the device are performed by either or both of a pair of Stewart platform manipulators.[208,2321] Each manipulator consists of a tool chuck mounted via universal joints to 6 telescoping struts mounted at their base to universal joints affixed to the interior face of the elevator block. Each strut is a matched pair of internally-threaded and externally-threaded tubes, whose capstan-driven relative helical motion extends or retracts the strut. An additional 7th control strut allows interchangeable tool tips to be grasped or released by the tool chuck.
7. **Control Chain.** The control chain consists of a single flexible molecular ribbon with a number of graphitic knobs integrally affixed to known positions along its length. A latchlike mechanism at the end of the piston rod engages the chain, converting piston-driven axial rod motion to transverse chain motion and forcing the chain to move. All normal operations use two pressure bands — an upper band from 2-3 atm and a lower band from 1-2 atm. The chain engages latching mechanisms at the control capstans of all elevator worm screws and Stewart platform struts. Cycling across the upper band steps the control chain forward, applying power to successive control capstans. Cycling across the bottom band steps the control chain backwards, but without applying power to any control capstans. Cycling across both bands (from 1-3 atm) causes the control chain to step back and forth over the same control capstan, repeatedly applying power only to that one control capstan.
8. **Tool Garage, Tools, and Tool Tips.** A complete set of molecular tool tips[1,216,2322-2325] sufficient to perform all required mechanosynthetic functions during replication and product manufacturing, including diamond fabrication and deconstruction, hydrogenation and dehydrogenation of surfaces, and tool tip recharge and fabrication are stored in the garage. Graspable jigs for operating molecular import/export mechanisms, controlling extrusion, or extending van der Waals cages are stored in the tool garage, all within reach of the Stewart platform manipulators.
9. **Subassembly Stations.** Several areas designated as subassembly stations include wall-mounted active tips, fixed jigs, and other mechanisms by which intermediate structures can be temporarily parked during fabrication, either to allow more efficient execution of manufacturing sequences or to allow more complex assembly operations such as insertion motions.
10. **Extrusion Control System.** Manufacture of product object proceeds downward from the extrusion hole towards the opposite floor. When sufficient fabrication has been completed, the workpiece is ratcheted upward a controlled distance by sequentially pulling spring-loaded locking pins out of their staggered complementary pinholes in the exterior face of the workpiece and re-inserting them into the next-lowest pinhole in the workpiece exterior face. This provides a controlled extrusion process, provides mechanical resistance to hydrostatic backpressure and oscillatory acoustic forcing, and ensures that extrusion takes place even if resisted by significant external forces.
11. **Van der Waals Cages and Pegs.** Multiple devices whose smooth, flat parallel surfaces approach too closely will be attracted to each other by van der Waals forces, in some cases noncovalently bonding into randomly-ordered aggregates. To prevent such surface bonding and consequent blockage of the I/O wall and the piston wall, two cages of rods configured as wire-frame boxes

are extended into the external environment from the I/O and piston walls, as soon as physically possible. Short spring-loaded pegs also deploy from the outer face of the locked piston on extruding daughters and granddaughter devices (or the equivalent face for other product objects) as soon as physically possible, thus geometrically lessening surface attractive forces and reducing any attractive interdevice forces that might resist extrusion.

12. **Passive Hull System.** The vast majority (~90%) of all carbon atoms present in the Merkle-Freitas Hydrocarbon Molecular Assembler constitute the 10-nm thick solid diamond hull. This passive hull is penetrated by three openings for materials import/export (I/O wall), by the piston plate at the opposite end (piston wall), by van der Waals cages at either end, and by the extrusion hole in which the daughter device or product object resides while it is being fabricated and extruded.

4.12 Bishop Overtool Universal Assembler (1995-1996)

In 1995-1996, Bishop[825-828] proposed the "Overtool Universal Assembler" (Figure 3.20) as a system of kinematic cellular automaton (KCA) active cells (Figure 3.18) that could assemble individual KCA cells from more primitive parts.[828] Each of the KCA cells are cubic machine blocks called "XY cubes" measuring ~167 nm on an edge in the baseline design. The cube structural material is asserted to be diamondoid. Each active cell contains an embedded digital controller to allow communication between blocks and to perform other housekeeping functions, and an internal electromechanical interface switch for power and signals. Energy is delivered to the cell electrically, via sliding contacts, and the drive system is a type of linear electrostatic motor in which dielectric material is successively drawn into the gaps between the two plates of a switched row of capacitors.

When two XY cubes are interfaced and aligned, four tapered, retractable locking pins extend from one cell to complementary receivers in another cell, locking the two cubes together. The mechanical interfaces consist of orthogonal T-slots cut into the face of a cube. Each cube has an active faceplate on three of its adjoining faces, and passive faceplates on the other three faces. (The issue of van der Waals adhesion was mentioned but not seriously addressed in the paper.) These geometric features introduce a chirality to any aggregate of XY cubes, along with a specific orientation for mutual interfacing. Cube rotation is not permitted, so this internal organization is maintained regardless of the configuration of the aggregate. An active face is always adjoining a passive face as cubes slide against one another. A "motion primitive" is a single cell move across one cell length, with the moving cell beginning and ending in the aligned rest position. Multiple motion primitives applied to many cubes in many directions can produce complex movements and shape changes of the aggregate.

The Overtool itself is an active cell aggregate — a space-filling polyhedral aggregate with internal sliding planes and manipulators on the faces of some of the cells. "The essence of this proposal," Bishop explains, "is to reduce the number of individual parts (the cells) to a small set of identical components governed by a few simple rules of interaction. A collection, or aggregate, of these cells then forms a device of arbitrary size which can change its configuration to fit the desired task. The active cells and nanomanipulators are further broken down into a set of standardized parts. The assembler may be capable of making and assembling all of these parts, thereby replicating itself." The Overtool aggregate would "provide the necessary functionality, variability, and means of transport to form the core of a universal assembler, for macroscopic assembly as well as for positionally controlled chemical synthesis."

4.13 Goddard Proposed Assembler Simulation Study (1996)

In 1996, William A. Goddard and colleagues[2327] proposed a series of molecular dynamics simulations of simple assemblers, as part of their Computational Nanotechnology Project at the California Institute of Technology, although by 2001 funding for the assembler studies had not yet materialized. According to Goddard's original proposal:

"Dynamic tests of a molecular assembler. Ultimately we need a programmable synthetic system to make a real device. Even though we may not have tools for all the chemical steps and may not have designs for all the pumps, engines, and transmissions needed, we propose to study the dynamics of simplified prototype assemblers. In these studies we anticipate having (1) a reservoir or supplies area for providing the various building units (atoms and fragments) required, (2) a work area in which we construct the nanomachine device (initially we will consider assembling the structure on top of a diamond surface), and (3) a molecular scale nano-hand which will extract the atoms from (1) and carry them to (2). We will then use extensions of our MPSim massive molecular dynamics program to operate the system: moving the tip from reservoir to work area, moving it to contact the appropriate surface site, moving it to regenerate the active tip, and then moving it back to add new atoms and molecules. This will include proper temperature effects, molecular vibrations, energy release upon the various chemical steps, etc. The ground rules here are that a realistic force field be used and that all pieces be treated at the atomic level (but some might be semi-rigid). This will use the force field developed for nanosynthesis. The purpose of these simulations is to examine issues of vibration caused by chemical forces as the tool picks up and delivers atoms to the growing surface. Also we want to consider the effect of energy release in the chemical steps on the thermal fluctuations in these systems (which may cause displacements and vibrations)."

4.14 Zyvex Nanomanipulator Array Assembler System (1997-1999)

An early assembler system design appeared on the Zyvex Corp. website during 1997-1999,[2328] and in a different version in 2000,[2329] and read, in part, as follows:

"Our idealized assembly process starts from a Computer-Aided Design (CAD) description of some object to be built. Computer-Aided Manufacturing (CAM) software decomposes the object into primitive building blocks and then into an assembly sequence. The assembler control computer uses this assembly sequence to control a huge number of nanomanipulators performing mechanochemistry to build the desired object. Each nanomanipulator may only be capable of moving a single molecular scale building block around, but since there are a huge number of these nanomanipulators working simultaneously, the system is capable of building a large quantity of products.

"The assembler differs from both semiconductor manufacturing and bacteria in that it operates on some atomically precise molecular building blocks to build precise structures of arbitrary complexity, as specified by a CAD/CAM program. Very simplistically, it could be a bank of molecular-scale robotic arms with chemical binding sites on some arms, and grippers to hold components being built on another set of arms, all under the control of an outboard computer instructing it how to move to snap together the building blocks for the desired product. The assembler control computer totally controls the product being built, driving the manipulators to execute the sequence of motions specified by the manufacturing software. In the morning, this assembler might make computer memory modules; in the afternoon, it might make medical manipulators; later it might be programmed to build power storage devices.

"The initial assembler will not include an onboard computer or power source for the manipulator, so must be controlled and powered from outside the device. The system design required for a practical assembler must deal with how to get power and signal into a huge number of nanomanipulators, as well as how to get feedstock to them and take finished materials away after construction. [One] approach would be to anchor nanomanipulators on a substrate that could provide power, control, and a transport system for materials. Such a system could move a large number of manipulators by moving the substrate, and thus could build objects much larger than itself in all dimensions.

"This first assembler can be a crude device; its purpose is to show that molecular nanotechnology is feasible, and to build a better device. For rapid improvement, the manufacturing system must be capable of being improved by the products it manufactures. A semiconductor manufacturing plant cannot manufacture itself, hence the cost of a semiconductor production line goes up with each generation, and is now nearly unaffordable. A well-designed nanotechnology manufacturing plant should not suffer from this problem, since it will be built using the same technology and techniques it is using to manufacture other goods.

"The last point is important enough to restate. A practical design for an assembler requires the assembler to be made from materials it can handle. With this closure, assemblers can be manufactured as inexpensively as the products they make. This capability is often called self-replication, although we prefer the term exponential assembly, which is less likely to be confused with living entities. Living systems carry their own instructions in DNA, while exponential assembly does not. Exponential assembly devices must receive instructions from a conventional computer control system. This system design is both simpler and safer."

4.15 Bishop Rotary Assembler (1998)

In 1998, an illustration (Figure 4.46) and an animation[2330] of one possible version of a nanomanipulator array assembler system was conceived and designed by Forrest Bishop of Interworld Productions.[2330] The XY table with a putative buckytube STM tip might possibly have been inspired by a Zyvex illustration or by the written description of the proposed Zyvex array assembler system (Section 4.14), as its operation is somewhat similar.

According to Bishop:[2331] "The upper platter holds bulk-deposited molecules or moieties. An array of massively-parallel simple manipulators removes the molecules from the upper platter and adds them to devices being assembled on the lower platter. Different areas of the feedstock platter might have different kinds of molecules, such that several assembly steps can be carried out before having to change out the upper platter. The conical roller moves radially, while the upper platter moves up and down, to access these different areas. The STM tips would have some ability to compensate for the slippage of the roller as the tip reaches for its target."

4.16 Hall Factory Replication System (1999)

Following in the intellectual lineage of the 1980 Freitas factory replication system (Section 3.13.2.2) and the 1991-1992 Drexler factory replication system (Section 4.9.3), in 1999 J.S. Hall published a general design[225] for a self-replicating molecular manufacturing system that is likewise composed of specialist machines, each one individually incapable of full self-replication but which can collectively fabricate and assemble all necessary components comprising all specialist devices within the system. Whereas the Freitas factory design employs three main classes of specialist production machines (i.e., chemical processors, parts fabricators, and parts assemblers),[2,1014] and the Drexler factory design employs a succession of manipulators at increasingly larger scales (i.e., molecular fabricators, block assemblers, system assemblers),[208,2910] the Hall factory design simplifies the number of specialist machines to just two — a parts fabricator and a parts assembler:

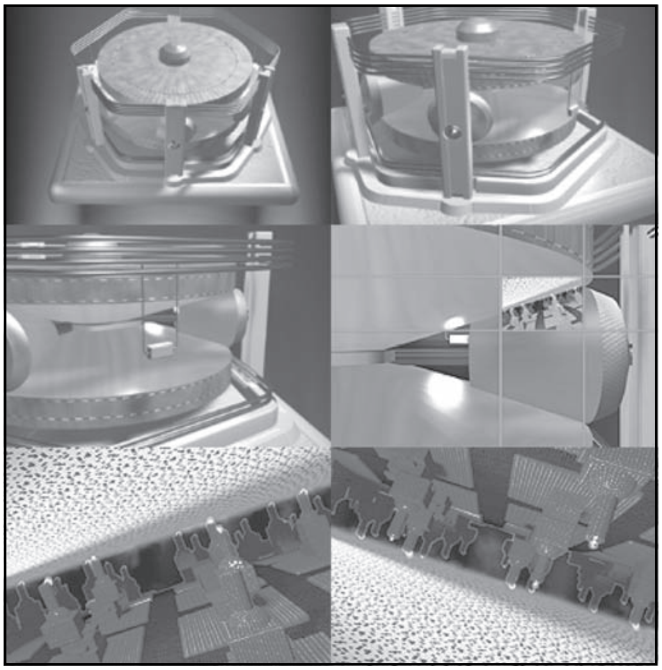


Figure 4.46. Rotary Assembler.[2330] One of the machines that will be possible using the new-found ability to manipulate single molecules and atoms is illustrated here. This vaguely CD-ROM-like machine assembles other nanomechanical systems by means of 5 degrees-of-freedom tips that pick molecules off the upper platter, rotate down and deposit them on the product arrays of the lower platter. (illustrations were a joint effort, and are provided courtesy, of Forrest Bishop (Interworld Productions, LLC) and Philip Van Nedervelde (E-Spaces); © 1998 Interworld Productions, LLC; all rights reserved)

The parts fabricator has the following attributes:

1. It has a work envelope smaller than, indeed probably within, itself.
2. It operates with atomic precision.
3. It makes parts which are single rigid objects with no internal configurational degrees of freedom (there may be an exception in the case of springs).
4. It might be able to create strained structures, though in general these are to be avoided as requiring additional manipulative mechanisms. (It may be possible to produce structures with dislocations by essentially chemical means, by virtue of the pattern of deposition reactions.)

The parts assembler, on the other hand, has these attributes:

1. It has a work envelope larger than itself.
2. It does not necessarily operate with atomic precision; parts can be made to allow compliant assembly.
3. It assembles parts into mechanisms which have multiple internal degrees of freedom.
4. It will be capable of exerting mechanical force to tension springs, snap snaps, and otherwise move the constructed system across energy barriers.

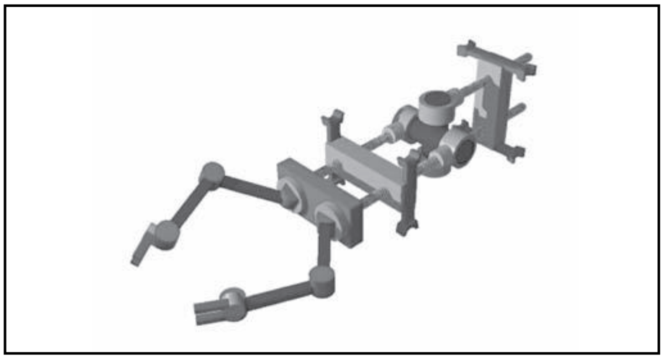


Figure 4.47. A motile parts-assembly robot in Hall factory replicator.[225] (courtesy of J. Storrs Hall)

The above architecture greatly simplifies the design of the fabricator because the objects it builds are rigid. This allows the fabricator to address reaction points on the surface of the partially-built product object without concern for whether the object has undergone a configurational change. It relieves the fabrication design process from the necessity of scaffolding, its provision and subsequent removal, simplifying the process and making it easier to maintain a eutactic environment. In the early stages, the system is assumed to be in a eutactic environment (possibly a non-reactive atmosphere). In later stages it may take on the task of extending the environment (e.g., with a balloon over the framework). Hall has described the components of his factory replicator in more detail:

The parts assembler. The parts assembler consists of two elements — first, a parts-assembly robot (Figure 4.47) that is, except for its motility, consistent with the currently well-understood practice of parts-assembly robots; and second, a framework to move in (Figure 4.48) that provides precise positioning and traction (the problem of motion control is relatively modest). The salient features of the parts-assembly robot include its ability to engage, move, and turn in the framework, and the fact that it has two manipulators (although a judicious selection of jigs and clamps may obviate the duplication and permit a one-armed design). The outward clamps at the rear and near the geometric center of the robot engage the struts of the framework. This provides not only physical support but positional registration, as well as power and control signals. The earliest generations of these robots will have no onboard control but will obey signals transmitted across the framework. The framework itself is a simple rectangular 3-dimensional mesh, originally with conductive paths for only a single circuit. In the earliest generation, the entire framework is one interconnected multiconductor system. In subsequent generations, switching elements are built into the connectors and multiple conductive paths are incorporated into the struts. "Ultimately, the framework is a distributed control system coordinating the activities of large numbers of robots, as well as forming the physical infrastructure for the target product." This would appear to restrict buildable products to those objects which can tolerate the permanent internal embedding of 3-dimensional electronic meshworks. Also, it is not clear from the discussion whether the parts fabricators and parts assemblers themselves incorporate such meshworks.

The parts fabricator. The parts fabricator (Figure 4.49) is loosely based on a conventional milling machine, with long motion axes all driven by lead screws and the motions of the wrist (Figure 4.50) to orient the working tip driven by high-reduction-ratio steppers with short working radii. The parts fabricator uses similar motor and control structures as the assembly robot, but these are arranged to deliver more precise (but thereby slower and shorter) positioning capability. In theory, a 4-position (2-phase) stepper with a 50-to-1 reduction driving a 2-nm pitch lead screw (i.e., 1-nm lands and 1-nm grooves) can position a slider with a precision of 0.01 nm (which is sufficient for mechanosynthesis), and the parts can be assembled correctly by a manipulator with only 0.10-0.25 nm precision. "A problem that does not appear to have been addressed to date is that of starting the deposition process. A possible approach would be 'starting blocks,' which would be small blocks of diamondoid material provided as raw material (just as working tips would be). The table (Figure 4.49) would be tessellated with cavities of an appropriate shape to bind the starting blocks reliably. Once the part had been fabricated, it would be removed from the table by the application of mechanical force by an assembly robot. The assembly robots would also position the starting blocks initially and provide the fabricator with a stream of working tips in early versions. (Note that self-assisted assembly,* together with appropriate jigs and limit stops, allows the robot to place the tool precisely in the synthesizer's manipulator.) An openwork truss can have a high

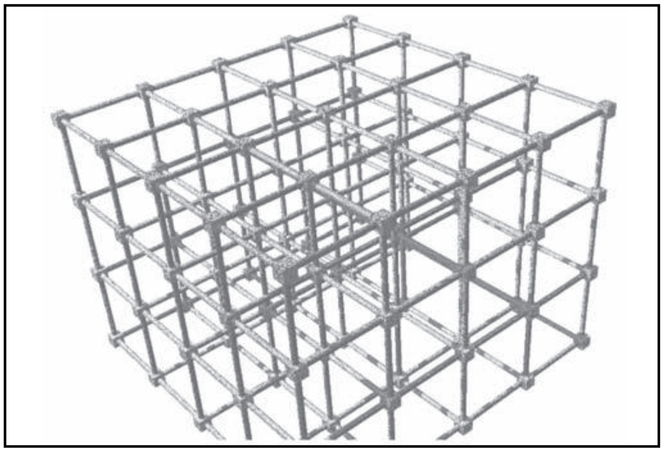


Figure 4.48. Rectangular 3-dimensional framework for parts assembly in Hall factory replicator.[225] (courtesy of J. Storrs Hall)

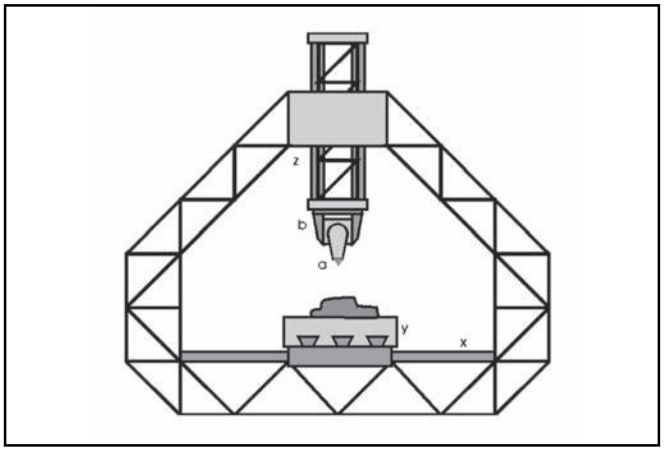


Figure 4.49. Parts fabricator in Hall factory replicator.[225] (courtesy of J. Storrs Hall)

---

* *Self-assisted assembly, like guided or directed self-assembly (Section 4.1.5), represents a halfway point between full positional assembly and full self-assembly — as for example, a screw which, when pressed to a hole and axially pushed forward, screws itself into the hole.*

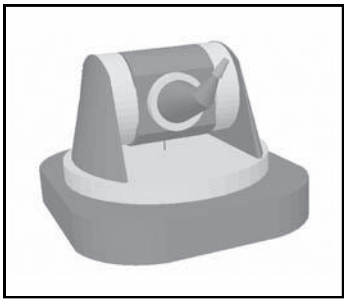


Figure 4.50. A detailed view of the wrist assembly of the parts fabricator in the Hall factory replicator.[225] (courtesy of J. Storrs Hall)

stiffness-to-mass ratio, and can be easily assembled from smaller parts. In this design (Figure 4.49), there are three axes of motion consisting of sliding dadoes driven by lead screws. There are three axes of orientation at the wrist for the mechanosynthetic active tip. The bend in the toolholder (Figure 4.50) allows a greater range of access to the typical object under construction than a straight one would."

Another interesting aspect of Hall's design is his concept of a pre-planned sequence for "iterated design bootstrapping." Whereas bootstrapping had previously been considered in other contexts (Section 3.9) — for example, Freitas[1014] had advocated a basic two-step bootstrap in which a simple seed would build a complex factory, which factory would then build the desired large output product, a space probe (Section 3.11) — Hall[225] discussed a multi-step process that might be the optimal overall approach to bootstrapping replicators: "Suppose we have a series of designs, each some small factor, say 5.8, more complex, and some small factor, say 2, faster to replicate, than the previous. Then we optimally run each design 2 generations and build one unit of the next design. As long as we have a series of new designs whose size and speed improve at this rate, we can build the entire series in a fixed, constant amount of time no matter how many designs are in the series. (It's the sum of an arbitrarily long series of exponentially decreasing terms — perhaps we should call such a scheme 'Zeno's Factory.')" If the simplest possible factory replication "seed" system is assumed to be composed of $\sim 10^7$ atoms and requires $\sim 10^5$ sec for replication, and the most complex system "with fully pipelined parts assembly" is assumed to include $\sim 2 \times 10^{12}$ atoms with a replication time of 2×10^{-3} sec, then the bootstrapping sequence from simplest to most complex system runs through ~25 successively improved factory designs. "With the appropriate series of designs starting from the simple system above, the asymptotic limit is a week and a half (e.g., ~100 hours for design 1 to build design 2, followed by 50 hours for design 2 to build design 3, plus 25 hours for design 3 to build design 4, etc.) Since all the designs need to be ready essentially at once, construction time is to all intents and purposes limited by the time it takes to design all the replicators in the series."

Hall's exemplar bootstrapping sequence would start with "a small framework, one assembly robot, and a pile of parts," and would progress through a series of four factory configurations, labeled "I" through "IV" in Figure 4.51. These would result in a more complex factory system differing dramatically from the first, with "each of the processes of the earlier stages taken over by specialized machinery. Pipelined processes (i.e., assembly lines) do the building, while pipes, conveyor belts, and, ultimately, vehicles do the moving. A fully-functioning fourth-stage system can discard everything that comprised the second stage system."

4.17 Zyvex Exponential Assembly (2000)

At the micron scale, using existing MEMS (microelectromechanical systems) technology, Zyvex Corp. has designed simple pick-and-place robotic arms that could pick up relatively complex, planar, micron-scale parts made using lithographic techniques and then assemble those planar parts into simple three-dimensional robotic arms that have the ability to pick up specially designed MEMS parts. In Zyvex's Rotapod^{TM} exponential assembly design,[576] this replicative technology starts with a single robotic arm on a wafer (Figure 4.52) that makes a second robotic arm on a facing surface by picking up miniature parts — carefully laid out in advance in exactly the right locations so the tiny robotic arm can find them — and assembling them (Figure 4.53). The two robotic arms then make two more robotic arms, one on each of the two facing surfaces. These four robotic arms, two on each surface, then make four more robotic arms. This process continues with the number of robotic arms steadily increasing in the pattern 1, 2, 4, 8, 16, 32, 64, etc., until some manufacturing limit is reached (e.g., both surfaces are completely covered with tiny robotic arms). This is an exponential growth rate, hence the name exponential assembly, but the assembly process requires (among other things) lithographically produced parts as well as externally provided power and computer control signals to coordinate the complex motions of the robotic arms. Thus this approach is an example of both the broadcast architecture (for instructions) and the vitamin architecture (for parts and energy) being employed in a single system. As a result, this system is *very* "inherently safe" (Section 5.11).

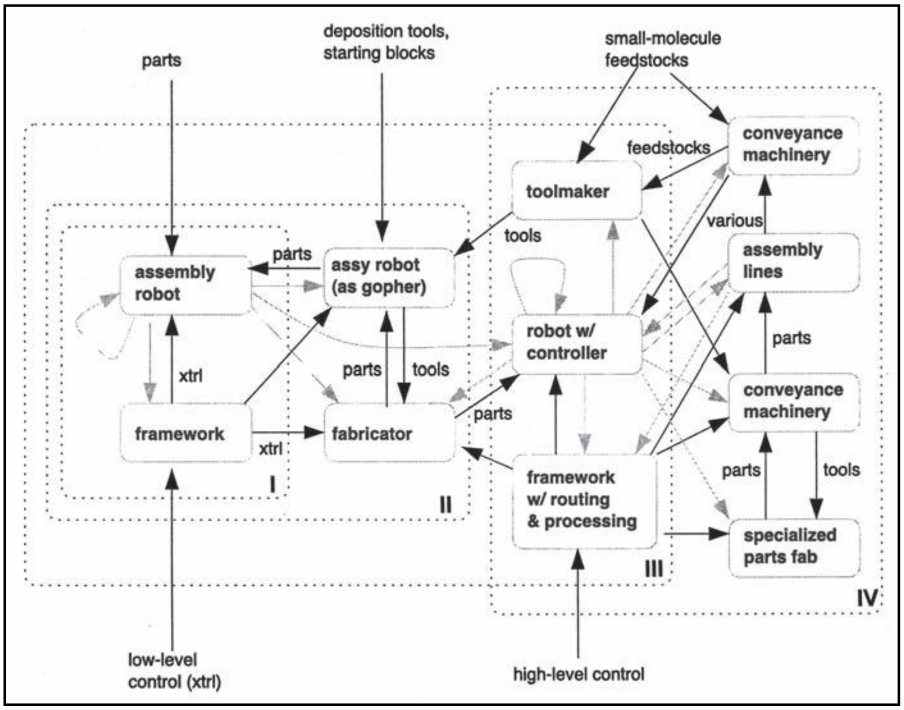


Figure 4.51. System diagram for the bootstrap path of a self-replicating manufacturing system.[225] (courtesy of J. Storrs Hall)

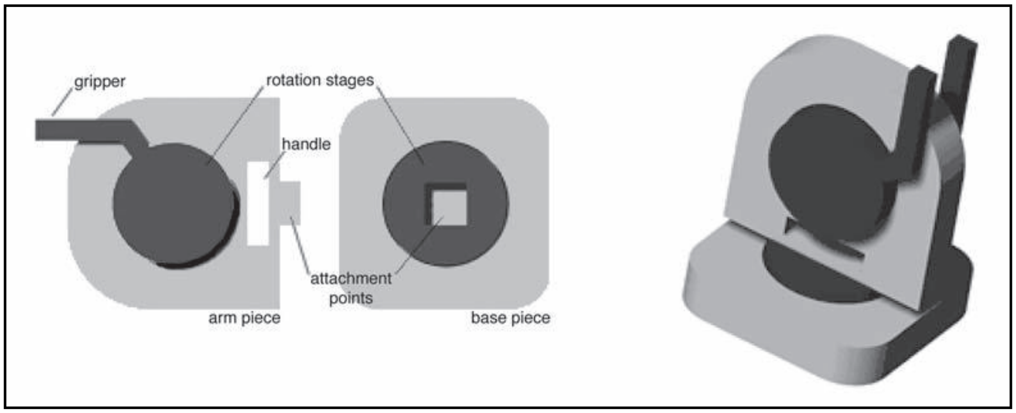


Figure 4.52. Basic two-component Rotapod^{TM} assembly station.[576] Left: The rotational stages are labeled as are the gripper, handle, and attachment points. Right: When the two components are assembled, the assembly station is as shown. (courtesy of Zyvex Corp.)

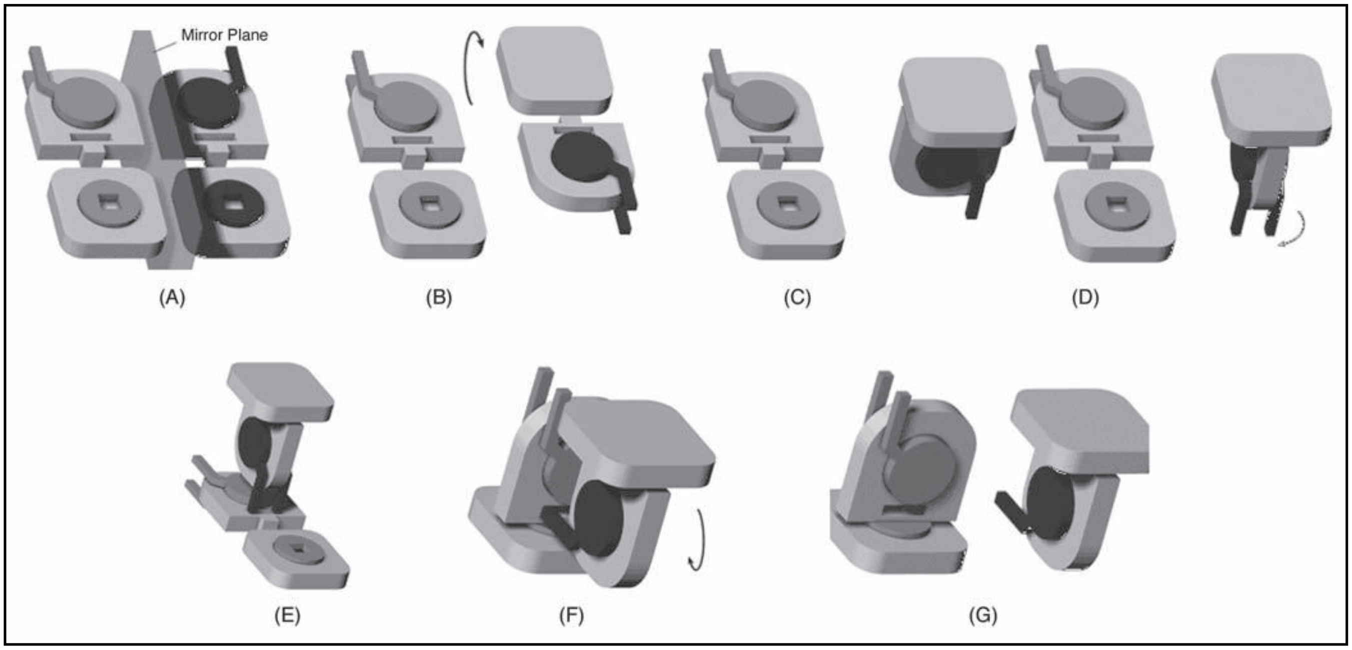


Figure 4.53. Sequence of Rotapod^{TM} assembly operations necessary for the first station to assemble the second.[576] (A) The stations are first shown unassembled. (B) After rotating one of the stations, the two are shown facing each other. (C) The first is then assembled. (D) The assembled station first rotates about the z-axis. (E) It then translates to grip the component of the other. (F) The second rotation stage of station one then rotates 90 degrees and the surface then translates such that the attachment points are aligned with translation. (G) After the attachment is made the gripper releases and the assembly is completed. (courtesy of Zyvex Corp.)

While a general purpose robotic arm having six degrees of free movement (like human arms and hands) would be able to pick up parts and position them in any orientation and position desired, such a general purpose arm is harder to make. Zyvex's simpler Rotapod^{TM} design uses robotic arms having only two rotational degrees of freedom and a gripper (Figure 4.52), while offloading three degrees of freedom to the external environment: the surfaces on which the parts are arrayed can be moved in X, Y and Z, providing a total of five degrees of freedom for each robotic arm, with the three translational degrees of freedom being shared across all the robotic arms on a surface. Externally provided power and computer control cause all the robotic arms on a surface to operate synchronously and in parallel.

Exponential assembly can be implemented on many different length scales. Given existing manufacturing capabilities, it should be possible to implement exponential assembly using MEMS technology with device sizes measuring tens or hundreds of microns and feature sizes of about one micron. Each rotational degree of freedom could be implemented using a planar rotating stage produced using standard lithographic techniques. Two such rotating stages can be attached at right angles, providing the desired two degrees of rotational freedom for this assembly station. A gripper attached to one rotating stage completes the basic design. Assembly of the first robotic arm could be done manually using Zyvex's MEMbler™ conceptual MEMS assembly station.[2332] Having assembled the first robotic arm, the Rotopod^{TM} could then assemble further robotic arms in exponentially increasing numbers (Figure 4.54), as illustrated in an animation.[2333] In 2003, a patent "Method and System for Self-Replicating Manufacturing Stations" (#6,510,358) for this manufacturing system was issued to Zyvex by the U.S. Patent Office.[273] A crudely analogous electrophoretic system for stepwise exponential growth of DNA-based chemical replicators using pairs of alternating opposed deposition surfaces has been proposed by von Kiedrowski's group.[1362,1428-1430]

In 2001, Zyvex was awarded a $25 million, five-year, National Institute of Standards and Technology (NIST) Advanced Technology Program government contract — to develop prototype microscale assemblers using microelectromechanical systems

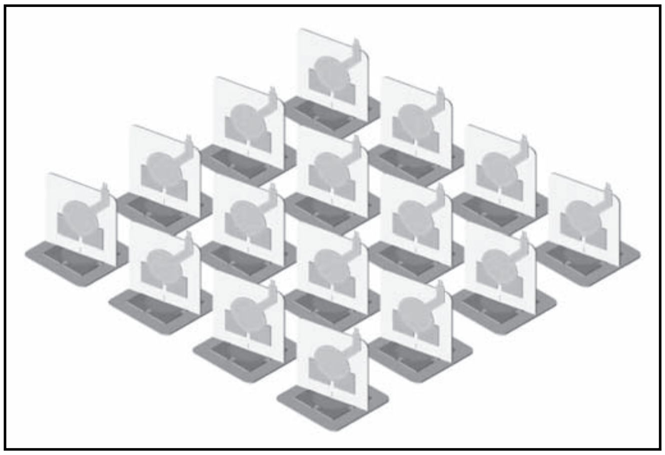


Figure 4.54. Result of five generations of Rotapod^{TM} exponential assembly operations (one completed robotic wafer shown, of two). (courtesy of Zyvex Corp.)

(MEMS), extend the capabilities to nanometer geometries, and then to develop nanoelectromechanical systems (NEMS) for prototype nanoscale assemblers.[2247] Along with its commercial partners and its university collaborators (Rensselaer Polytechnic Institute Center for Automation Technologies,[57] the University of Texas at Dallas, and the University of North Texas), Zyvex hopes to accelerate the production and commercialization of low-cost assemblers for micro- and nanoscale components and subsystems. The ultimate program goal through 2006 is nothing less than automated micro- and nano-manufacturing — the design and construction of assemblers capable of handling thousands of sub-micrometer components at high speed, using MEMS to prototype systems which could then be built at relatively low cost. Zyvex engineers are conceiving and testing various manufacturing architectures that someday might lead to the massively parallel construction of large batches of identical molecular machines simultaneously. This could allow vast numbers of nanodevices and nanorobots to be produced to precise molecular specifications, relatively inexpensively.

4.18 Freitas Biphase Assembler (2000)

Prior to his collaboration with Merkle (Section 4.11.3) during October 2000, Freitas sketched out a simple scaling study of a new molecular assembler architecture as a thought-experiment to demonstrate subunit specialization using individual replicator devices as an alternative to the more conventional specialized-subunit "factory production line" approach of Drexler's desktop assembler (Section 4.9.3) and Hall's factory replication architecture (Section 4.16). The biphase architecture also shows one way that the functions of fabrication and assembly performed by the Merkle-Freitas assembler (Section 4.11.3) could be separated into two distinct devices, possibly allowing faster operation and higher efficiency of the system as a whole although at the cost of some increased system complexity.

In the biphase assembler architecture, two classes of microscopic replicator devices cooperate in the manufacture of more replicator devices while freely suspended in a working fluid (either a liquid or a pressurized inert gas). Following Freitas' 1980 lunar factory replication concept (Section 3.13.2.2) in which the factory is divided into chemical processing, fabrication, and assembly subsystems (Figure 3.45), the biphase assembler is composed of (1) a population of identical fabrication devices that manufacture parts from molecular feedstock and (2) a separate population of identical assembly devices that manufacture fabrication devices and assembly devices from parts produced by the fabrication devices. The fabrication devices can also manufacture some range of non-self parts and the assembly devices can assemble some range of non-self parts, so that the system can also manufacture some range of useful non-self products. Fabrication and assembly devices are of similar size, in the 0.2-0.5 micron range.

The **fabrication device** (Figure 4.55(A)) consists of a central fabrication chamber measuring 300 nm x 300 nm x 200 nm (in the X, Y, and Z directions). The left face of the chamber includes molecular feedstock import and waste export mechanisms (e.g., sorting rotors) and an acoustic power/control piston, and on the right face is attached a workpiece arm garage 125 nm deep. To the top and bottom faces of the chamber are attached a 125-nm deep fabrication arm garage for each of the two fabrication arms. The 150-nm deep parts ejection piston garage is attached to the front face of the chamber, and there are tight-sliding parts ejection doors on the rear face of the central chamber, hence the entire fabrication device will fit within a 450-nm cube.

During one cycle of operation, feedstock molecules solvated in the external fluidic environment are imported into the device and made available to two opposed mechanosynthetic fabrication arms which perform fabrication operations in a vacuum environment and can exchange and reuse tool tips stored in a recessed tooltip garage on the inside of the materials import wall. The workpiece is held in proper position and orientation by the workpiece arm. When fabrication of a part is complete, the two mechanosynthetic arms are retracted and stowed behind fluidtight doors, the tooltip garage is sealed off, the workpiece arm releases the part into the chamber interior and then stows itself behind fluidtight doors, the parts ejection doors open (flooding the interior with working fluid from the external environment), the parts ejection piston ejects all contents of the fabrication chamber (including flood fluids and the recently finished part) from the chamber, the ejection doors close tightly against the piston face, the ejection piston retracts (re-establishing a vacuum inside the fabrication chamber), and the fabrication device is ready for the next cycle of operation. Obviously the chamber interior must contain no ledges where a finished part could become wedged and prevent its own ejection, and numerous other practical design issues remain to be addressed (e.g., bakeout plus rotor-based getters might be needed to remove lingering contaminant fluid molecules from the chamber interior between each cycle; released finished parts must be chemically unreactive with feedstock molecules and working fluid; etc.). It is envisioned that a large population of fabrication devices residing in a microfluidic processing tank would manufacture a large batch of one type of part, after which the mixed population of devices and parts could be readily separated by physical filtration or gentle centrifugation with the pure fraction of finished parts shunted to inventory and the pure fraction of fabrication devices returned to the processing tank for the next cycle of operation, ready to produce more parts of the same or a different kind.

The **assembly device** (Figure 4.55(B)) consists of a large acoustic power/control piston in a (200 nm)^3 box with 15 nm thick walls and a 100 nm throw, giving a power input up to ~3000 pW with 1 atm pulses at 10 MHz. A power/control interface 50 nm thick transmits power and control signals to: (1) a parts acquisition mechanism (possibly including a special parts capture jig at the end effector) on the top face of the assembly device, and (2) three manipulator mechanisms including two assembly arms and one workpiece arm, all 100 nm in length, whose bases are positioned at the points of an equilateral triangle on the right face of the assembly device. With all manipulator mechanisms fully extended the entire assembly device would fit within a box of approximate dimensions 200 nm x 350 nm x 300 nm in the X, Y, and Z directions. All assembly operations take place in the external fluidic environment, at a location separate from the operations of fabrication devices.

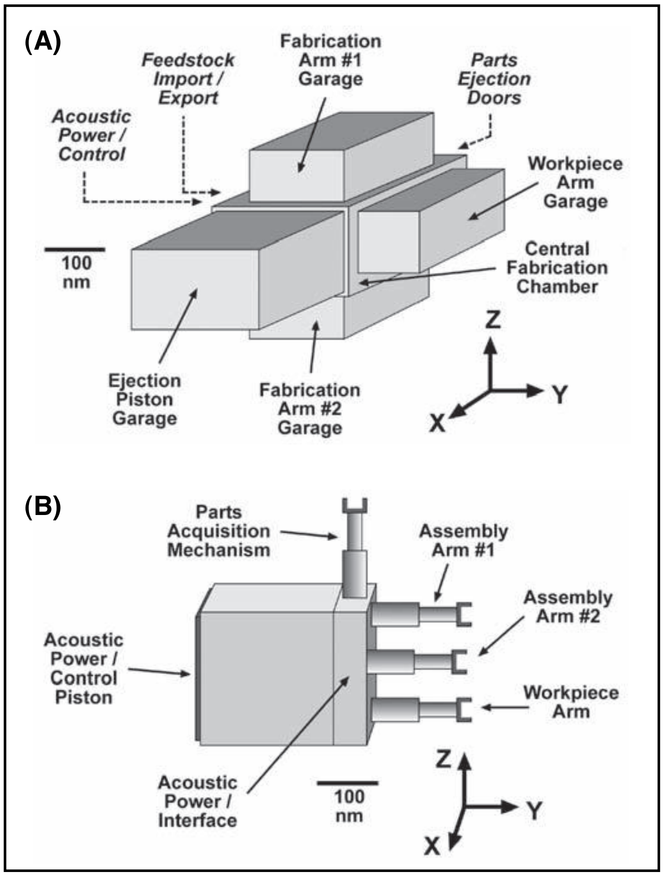

(A)
Feedstock Import / Export
Fabrication Arm #1 Garage
Parts Ejection Doors
Acoustic Power / Control
Workpiece Arm Garage
100 nm
Central Fabrication Chamber
Z
Ejection Piston Garage
Fabrication Arm #2 Garage
Y
X
(B)
Parts Acquisition Mechanism
Assembly Arm #1
Assembly Arm #2
Acoustic Power / Control Piston
Workpiece Arm
Acoustic Power / Interface
100 nm
Z
Y
X

Figure 4.55. Crude schematic of the fabrication device (above) and assembly device (below) in the Freitas biphase assembler system. (A) Biphase Assembler Fabrication Device. (B) Biphase Assembler Assembly Device.

During one cycle of operation, a feedstock part in fluidic suspension is mechanically recognized and grasped by the parts acquisition mechanism, then presented at proper rotation to the two assembly arms which install the part into the growing workpiece held at proper rotation by the workpiece arm. The presence of three manipulator mechanisms makes possible mechanically complex assembly motions such as pin-insertion operations through two separate components whose holes must be simultaneously aligned. Because of the negligible mechanical influence of gravitational forces, the assembly device should be able to grip and manipulate a workpiece as large as itself or even somewhat larger, with crucial enabling design elements such as number and placement of workpiece surface gripholds and assembly device manipulator armlengths subject to design control. The assembly device installs new parts, one by one, on the growing workpiece. If each of the assembly arms is similar to Drexler's fluidtight manipulator arm (Figure 4.29) and thus includes 49 parts (Section 4.9), and if we add an appropriate number of additional parts for end effectors, clutches, transmissions, odometers, power trains and the power/control piston assembly, and further assume 6 casing plates, then the assembly device is composed of a total of 430 parts and requires 429 assembly cycles to build a second assembly device. As with the fabrication devices, it is envisioned that a large population of assembly devices residing in a separate microfluidic processing vessel would first perform a large batch of one type of assembly operation in parallel, after which the mixed population of assembly devices with partially-completed workpieces attached and unused loose parts of one type floating in suspension would be separated by physical filtration or gentle centrifugation with the pure fraction of unused parts being returned to inventory and the pure fraction of assembly devices with attached workpieces being returned to the processing vessel, then mixed with a concentrated suspension of the next part type in the assembly sequence, in preparation for the next cycle of operation. Allowing 100 seconds per assembly cycle (including microfluidic separations) would give a replication time of ~0.5 day. (The fabrication device may possess up to twice as many parts and thus might require up to twice as many cycles for the assembly device to assemble it.)

The basic biphase assembler architecture could be further specialized by employing more than one class of fabrication or assembly device. In the limit of maximum specialization, using a separate class of fabrication device for each one of the many dozens of part types needed would allow each fabrication device to be optimized to achieve the most efficient manufacture of just one particular part type. Similarly, a separate class of assembly device could be used for each type of assembly joining operation that was required, essentially making assembly devices analogous to single-substrate enzymes in biology (e.g., "robozymes" or "mechanoenzymes"; Section 4.5). In principle, specialized assembly devices could perform covalent-bonding mechanosynthetic operations on parts to be joined, thus overcoming a key limitation of this architecture (viz., that fabricated parts must snap together during assembly in a fluid medium).

4.19 Phoenix Primitive Nanofactory (2003)

Recognizing that molecular manufacturing requires more than just mechanosynthesis, in 2003 Phoenix[2334] proposed a hierarchical system architecture for massively parallel assembly (Section 5.7) most directly in the lineage of the Drexler[208]-Merkle[213] convergent assembly nanofactory system (Section 5.9.4) at the early (smaller) stages of the hierarchy and the Drexler[208] nanofactory system (Section 4.9.3) in the later (larger) stages of the hierarchy. According to the principal published paper,[2334] the Phoenix architecture combines large numbers of programmable mechanochemical fabricators, under computer control, into a manufacturing system or nanofactory. In addition to physical layout, Phoenix's architecture and analysis includes some consideration of convergent assembly processes and simple mechanical connectors; thermodynamically efficient stepping drive mechanisms; redundancy and fault tolerance in fabricators and computers; product design, specification, and interpretation; product performance and cost; power budget, energy supply, and cooling; production, duplication, and bootstrapping times; and internal distribution of control information.

In a product cycle, each fabricator produces a 200-nm nanoblock, approximately the same size as the fabricator. (Blocks need not be solid cubes and their interiors may be quite complex.) These nanoblocks are then joined together, eight nanoblocks making one compound block twice as big. This process is repeated until the eight largest sub-product blocks are finally joined in an arrangement that is not necessarily cubical. The output of multiple product cycles may be combined to produce larger products. Products can be unfolded after manufacture, greatly increasing the range of possible product structures and allowing products to be much larger than the nanofactory that produced them.

At the lowest level, a few thousand **fabricators** are arranged in a planar workstation grid (Figure 4.56). Their products are picked up and assembled into progressively larger blocks by a series of increasingly larger robotic manipulators using guide rails and linear actuators. This plus a control computer constitutes a basic, reliable **production module** (Figure 4.57). In a production module, fabricators are positioned on two opposite faces, delivering their product nanoblocks to the interior. The nanocomputer occupies a third side, surrounding the product exit port. The remaining three sides may be closed by thin walls, but need not be closed at all between adjacent

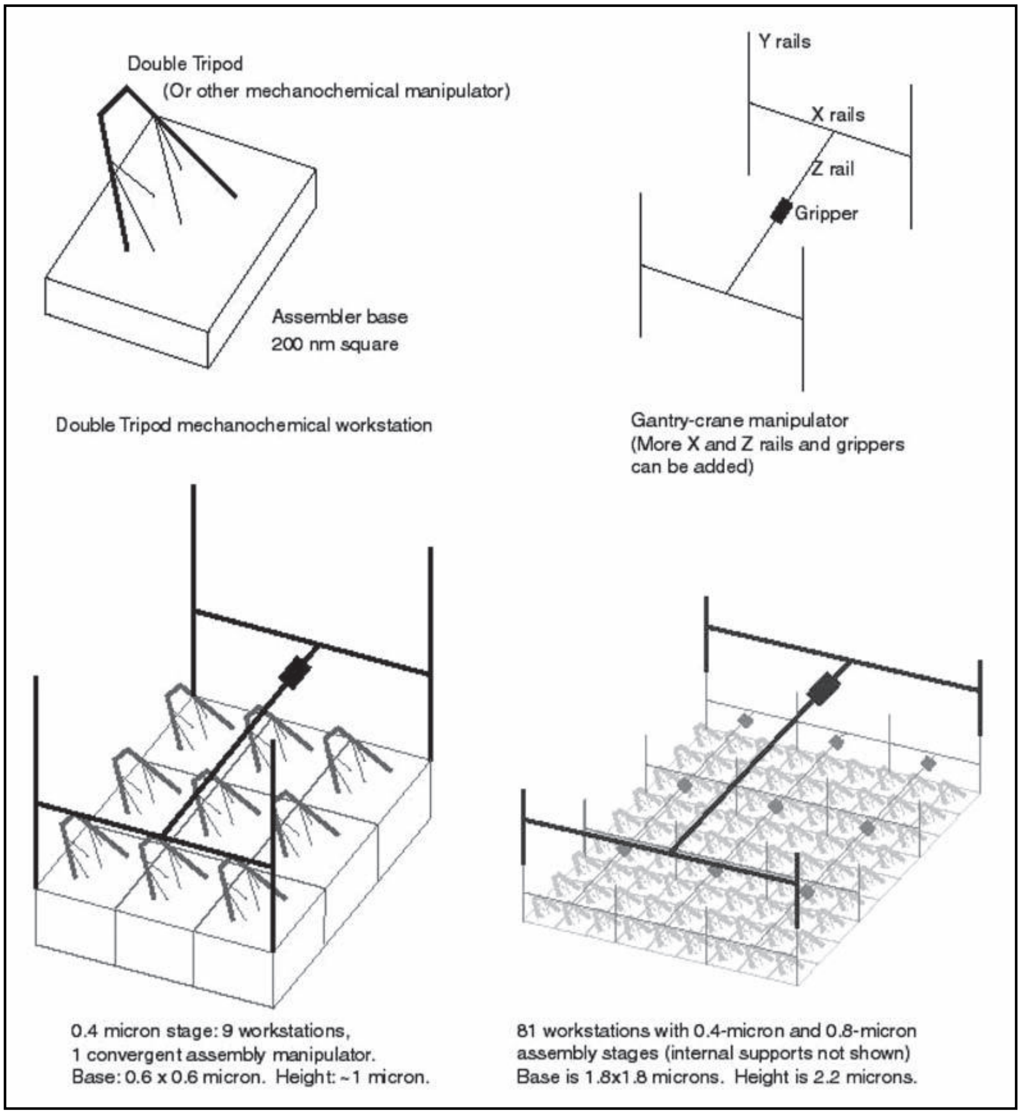

Double Tripod
(Or other mechanochemical manipulator)
Assembler base
200 nm square
Double Tripod mechanochemical workstation
Y rails
X rails
Z rail
Gripper
Gantry-crane manipulator
(More X and Z rails and grippers
can be added)
0.4 micron stage: 9 workstations,
1 convergent assembly manipulator.
Base: 0.6 x 0.6 micron. Height: ~1 micron.
81 workstations with 0.4-micron and 0.8-micron
assembly stages (internal supports not shown)
Base is 1.8x1.8 microns. Height is 2.2 microns.

Figure 4.56. Nanofactory workstation grid. (courtesy of Chris Phoenix[2334])

production modules. The interior is sparsely filled with gantry crane manipulators to assemble nanoblocks into larger blocks. Each production module produces a few product blocks, a few microns in size, by combining a few thousand nanoblocks. The production module includes multiple redundant fabricators interspersed throughout the fabricator arrays to permit multiple levels of fault tolerance in the event of fabricator failure or mechanochemical error.

Production modules are stacked three-dimensionally into **gathering stages**, which assemble blocks and pass them to higher-level gathering stages (Figure 4.58). Each gathering stage fits neatly into a rectangular volume, with substages arranged in two rows on either side of a central assembly and transport tube. At each stage, product blocks are delivered through the center of the narrowest face, allowing compact stacking of multiple production modules or stages. The substages, themselves rectangular structures, fit together with no wasted space in each row. The gathering/assembly tube contains simple robotic mechanisms to join the incoming product blocks into larger product blocks and deliver them out the end of the assembly tube.[2334] Space must be wasted between the rows, adjacent to the central tube, because this is a physically simple architecture.

Because the nanofactory is built with primitive fabricators and control systems, it is expected to use a lot of energy and can be cooled using a working fluid containing suspended encapsulated ice particles as originally proposed by Drexler.[208] Molecular feedstock for mechanosynthetic processes is also dissolved in the working fluid. Gaps are left for fluid channels adjacent to the fabrication arrays of the production modules, providing each fabricator with direct access to feedstock and, if necessary, flowing solvent to remove waste. As production modules are stacked, the cooling channels line up — the overall arrangement is a quasi-fractal working volume interpenetrated by a non-fractal cooling channel volume. Power and signals are routed through the walls of the transport tubes, since the end of every transport tube touches the side of the next-larger tube. Each stage joins eight blocks to form one block with twice the linear dimension, so 19 stages are required to progress from a 200-nm nanoblock to a 10.5-cm product, plus one additional stage (a simplified gathering stage) that is used to transition from production modules to gathering/assembly stages.[2334]

Finally, the entire factory is enclosed in a suitable casing with a mechanism to output final product without contaminating the workspace. In the highest level nanofactory layout, the overall nanofactory shape is a rectangular volume (Figure 4.59). The exterior shell consists of six flat panels, with each panel: (1) providing support to anchor the interior and prevent the working volume from collapsing under atmospheric pressure, and (2) supporting each other. Panels are hollow and pressurized, held rigid and flat using internal tension members set at a slight angle. The design is easily scalable to tabletop size, with a ~1 meter factory producing eight ~5 cm blocks per product cycle. A tabletop nanofactory measuring 1 meter x 1 meter x 0.5 meters might weigh 10 kg or less (without coolant),

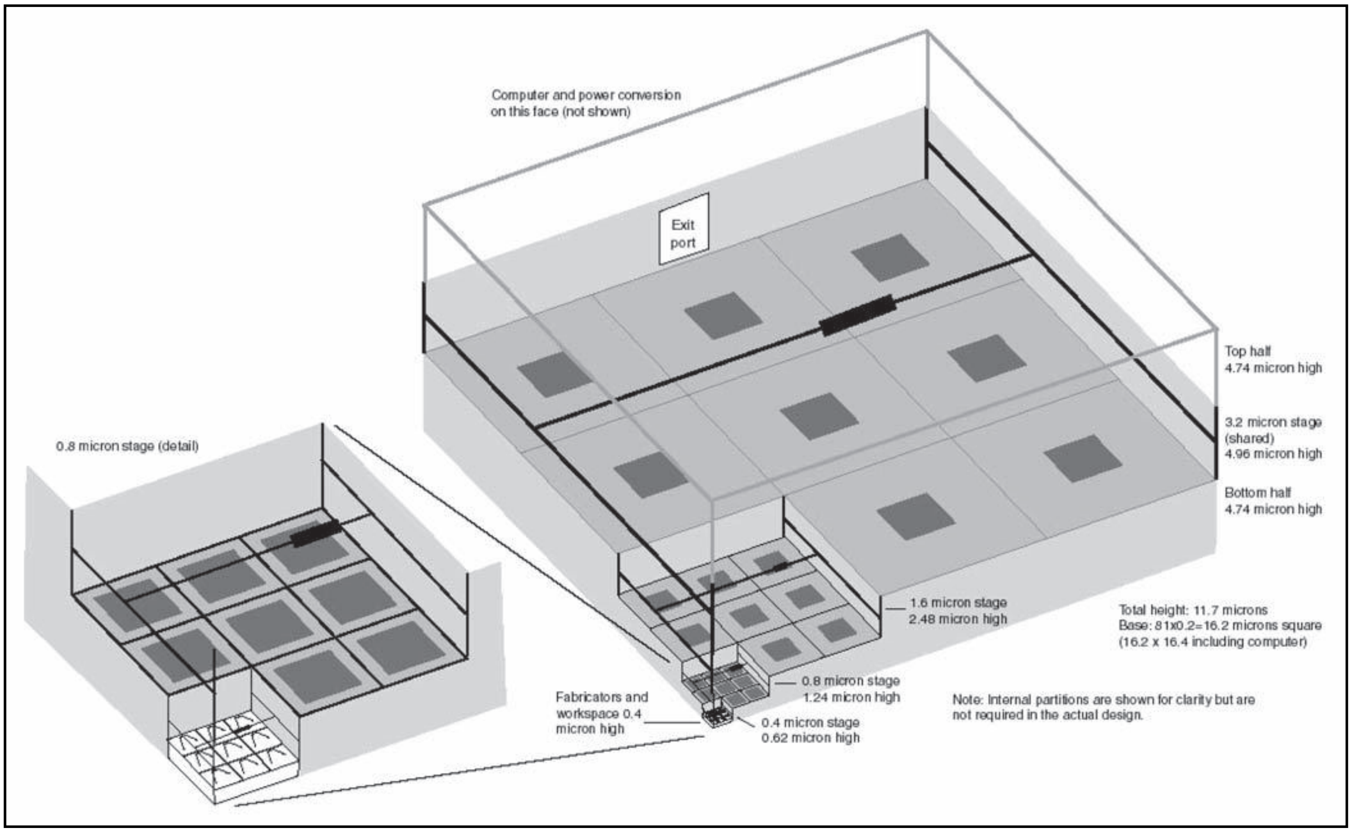

Computer and power conversion on this face (not shown)
Exit port
Top half 4.74 micron high
3.2 micron stage (shared) 4.96 micron high
Bottom half 4.74 micron high
0.8 micron stage (detail)
1.6 micron stage 2.48 micron high
Total height: 11.7 microns
Base: 81x0.2=16.2 microns square (16.2 x 16.4 including computer)
0.8 micron stage 1.24 micron high
Fabricators and workspace 0.4 micron high
0.4 micron stage 0.62 micron high
Note: Internal partitions are shown for clarity but are not required in the actual design.

Figure 4.57. The reliable basic production module. (courtesy of Chris Phoenix[2334])

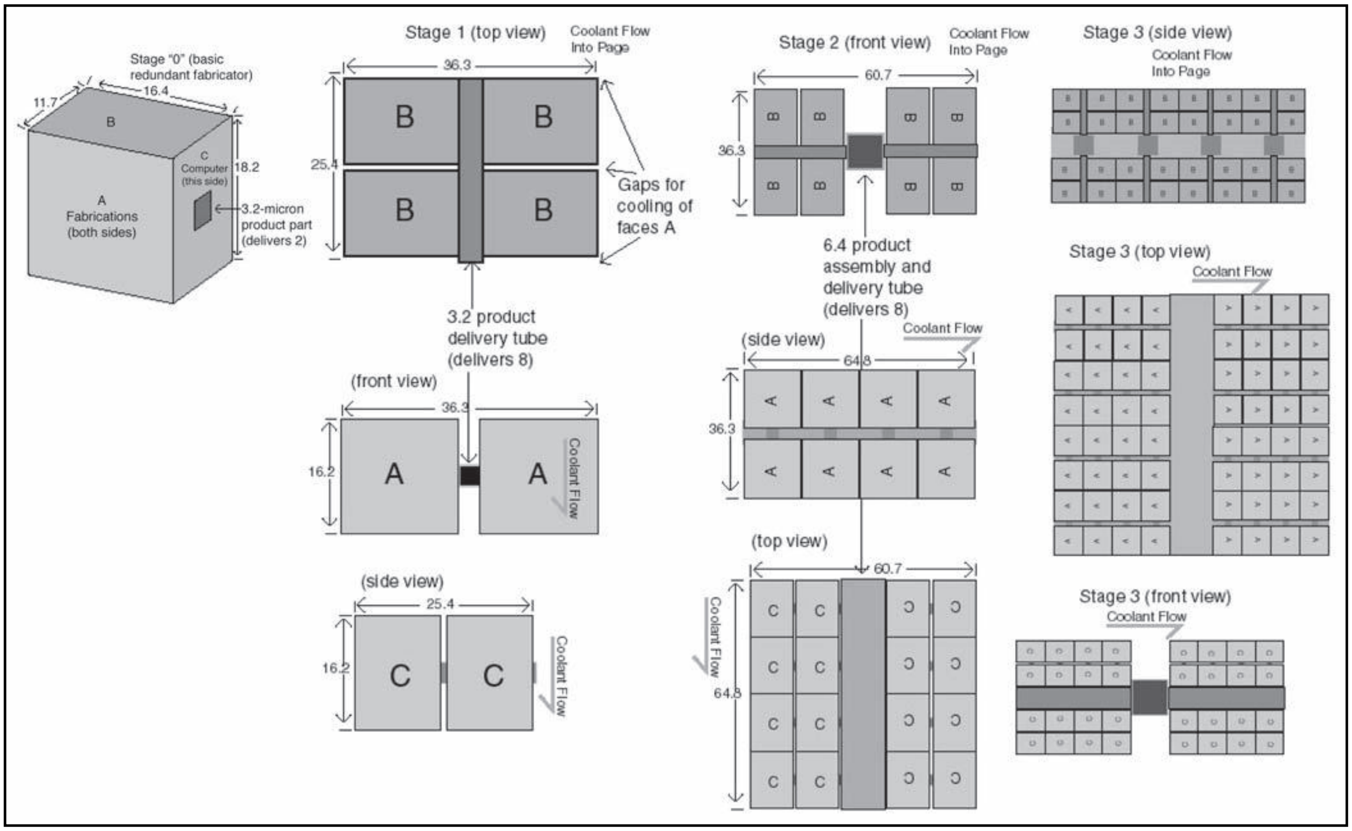


Figure 4.58. Convergent assembly fractal gathering stages. (courtesy of Chris Phoenix[2334])

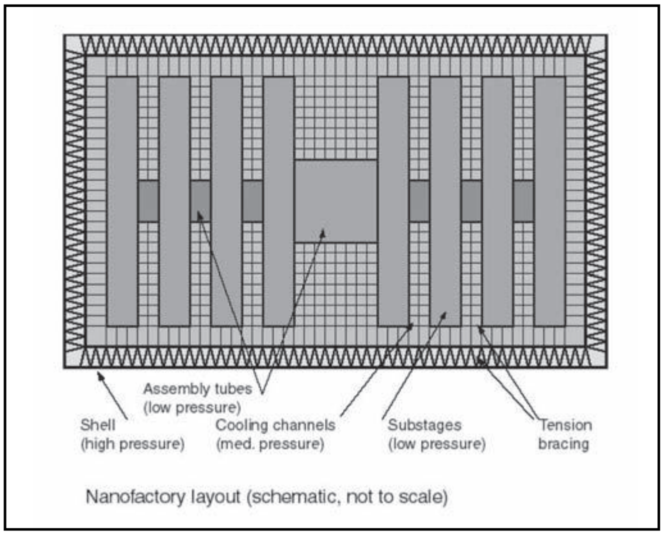


Figure 4.59. Casing and final assembly stage of nanofactory layout. (courtesy of Chris Phoenix[2334])

produce 4 kg of diamondoid (~10 cm cube) in 3 hours, and could require as little as twelve hours to produce a duplicate nanofactory.[2334]

4.20 Zyvex Microscale Assemblers (2003)

According to the new Zyvex corporate website[2248] in early 2004: "Zyvex Research Activities support both shorter term Product Development Projects and our longer-term goals of molecularly precise manufacturing."

"The NIST-ATP project will develop **prototype microscale assemblers** using MicroElectroMechanical Systems (MEMS), extend the capabilities to nanometer geometries, and develop NanoElectroMechanical Systems (NEMS) for prototype nanoscale assemblers. The program is structured to develop systems providing highly parallel microassembly and nanoassembly for real-world, high-volume applications. Zyvex proposed the NIST-ATP project in order to accelerate the technical, economic, and societal benefits of nanotechnology and to assist the United States in achieving a leadership position in the emerging nanotechnology arena. Other project participants are Zyvex's joint venture partner Honeywell International, Inc. and university collaborators Rensselaer Polytechnic Institute Center for Automation Technologies, and the University of Texas at Dallas."

"Zyvex's **Automation Project** seeks to develop automated manipulation and assembly of micro, nano, and molecular scale components, for applications ranging from research to high volume manufacturing. The project was initiated to develop the following capabilities:

- Automated precision assembly of millimeter and microscale components into unique systems (hybrid assembly)
- Automated manipulation of nanoscale and molecular-scale components for R&D of novel structures
- Microscale grippers, actuators, connectors, and automated systems
- Contract application development for precision automated assembly and manipulation techniques

The current capital equipment reality is that very high precision in assembly equipment demands a very high cost premium, and ever more elaborate schemes are required to assure system accuracy. Further, the macro schemes currently employed cannot deliver massively parallel processing. No firm has yet developed a cost-effective solution to this macroscale model, but microscale tooling has the potential to deliver a cost effective solution."

"Zyvex was founded to become the world's leading supplier of tools, products and services that enable adaptable, affordable, and molecularly precise manufacturing. Zyvex has been developing technology that will eventually lead to a **Molecular Assembler** technology. The Zyvex definition of a Molecular Assembler is 'a user-controlled fabrication tool capable of creating molecularly precise structures with 3-dimensional capability in an economically viable manner.' When it is brought to full fruition, this technology will revolutionize virtually all manufacturing technologies with the ability to produce machines and materials with molecular precision. However, we understand that a high throughput molecular assembler manufacturing technology is, in fact, a very long-term project. We have identified a path that will produce value as we work toward our long-term goal. In fact, all of the products and projects currently being pursued at Zyvex have been developed as a result of our efforts towards a Molecular Assembler. We have also identified a number of high-value, low-volume products that will be produced with prototype molecular assemblers that have very limited output capabilities. While we have spent considerable effort investigating molecular pick and place as an approach to a Molecular Assembler, we are exploring other approaches.

The Molecular Assembler Project currently consists of three coordinated efforts: Micro Automation, Molecularly Precise Tools, and Patterned Atomic Layer Epitaxy."

"The **Micro Automation** effort is a result of the realization that affordable molecularly precise manufacturing for many products will only be possible with massive parallelism. Parallel micro-assembly (being supported in part by our NIST-ATP) will develop both the system architecture needed to handle parallel assembly, and the assemblers at the microscale required to deal with the output of large throughput molecular assemblers. The parallel micro assembly technology we develop will provide huge value to Zyvex by lowering assembly costs of the microsystems being produced today by the microelectronics, telecommunications, and biomedical industries.

We undertook the **Molecularly Precise Tool Project** in order to deal with the significant limitations that current scanning probe tips and other molecular manipulation tools have placed on science and technology. We are convinced that nano and molecular manipulation technology will not get out of the research labs until molecularly precise tips and other tools are developed. We believe that molecular pick and place will not be viable until dependable molecularly precise tools are available.

The **Patterned Atomic Layer Epitaxy Project** will combine two known experimental techniques to produce atomically precise nanostructures. In our view, this is the best approach to a molecular assembler that can make reasonable progress before molecularly precise tools are available. When the Molecularly Precise Tool Project produces a superior tip for patterning, this will greatly improve patterned atomic layer epitaxy and enable its scale-up to large parallelism. However, such tools will also enable significant progress in molecular pick and place technology. Zyvex will constantly be evaluating the best path to a massively parallel molecular assembler."

According to CRN Executive Director Mike Treder,[2337] reporting from the "Imaging and Imagining Nanoscience and Engineering Conference" held at the University of South Carolina in March 2004, Zyvex CEO James von Ehr announced "that his company has a ten-year plan to build a molecular assembler, that is, a machine system capable of atomically precise manufacturing at the nanoscale. Of course, as he admitted, they had an earlier, even more ambitious plan that they've had to revise. But he said they learned a lot from that experience, and seems confident that this current effort has a good chance of success. The new Zyvex approach will combine top-down work in nanolithography with bottom-up designs in scanning probe depositional chemistry."

CHAPTER 5

Issues in Kinematic Machine Replication Engineering

Aside from specific instances of kinematic replicators reviewed in Chapters 3 and 4, and the classical theory of self-replication as outlined briefly in Chapter 2, a number of other issues arise in the context of the practical design and engineering of kinematic self-replicating machines.

Accordingly, this Chapter reviews various taxonomies of kinematic replicators (Section 5.1), including a presentation of the comprehensive new Freitas-Merkle map of the kinematic replicator design space (Section 5.1.9). Chapter 5 then discusses various definitional issues including replication time and replicator mass (Section 5.2), the minimum and maximum size of kinematic replicators (Section 5.3), the Efficient Replicator Scaling Conjecture (Section 5.4), the Fallacy of the Substrate (Section 5.5), closure theory and closure engineering (Section 5.6), massively parallel manufacturing (Section 5.7), simulation software (Section 5.8), and a primer on the mathematics of self-replicating systems (Section 5.9). The Chapter finally concludes with brief treatments of two important policy-relevant issues: replicators and artificial intelligence (Section 5.10) and replicators and public safety (Section 5.11).

5.1 General Taxonomy of Replicators

The somewhat controversial general theory of "autopoiesis"[455,2350] — literally "the creation (or production) of self" — and autopoietic machines[455,2351] may be of some theoretical and philosophical interest.[455-457,2352-2370] For example, the canonical definition of an autopoietic machine was given by Maturana and Varela[455] who originated the neologism in 1971 (though anticipated in 1922 by Bogdanov's "tektology").[2372] They define autopoiesis as a concise set of six highly abstract criteria that apply to a given systemic "unity" of components (with clarifications kindly provided by Randall Whitaker[2351]) as follows:

1. *the unity has identifiable boundaries, via interactions with the boundary.* Is it discrete? Does it exhibit "extent"? Can you circumscribe it? Can you specify where the unity stops and the environment begins?
2. *"...there are constitutive elements of the unity, that is, components of the unity."* Can the unity be seen as a set of "parts"? Do these "parts" comprise the whole?
3. *"...the unity is a mechanistic system, that is, the components' properties are capable of satisfying certain relations that determine in the unity the interactions and transformations of these components."* Is the unity capable of acting on itself?
4. *"...the components that constitute the boundaries of the unity constitute these boundaries through preferential neighborhood relations and interactions between themselves, as determined by their properties in the space of their interactions."* Are the components of the apparent boundary participating in that boundary as a result of their interrelationships and interactions? Are the components of the apparent boundary discernible as such because of their participation in the processes of the composite unity?
5. *"...the components of the boundaries of the unity are produced by the interactions of the components of the unity, either transformation of previously produced components, or by transformations and/or coupling of non-component elements that enter the unity through its boundaries."* Are the components of the apparent boundary produced by the processes comprising the unity itself? Is the unity generating the components (of this apparent boundary) either from existing components or through accreting elements it appropriates from its environment?
6. *"...all the other components of the unity are also produced by the interactions of its components as in (5), and ... those which are not produced by the interactions of other components participate as necessary permanent constitutive components in the production of other components..."* Are all the components of the unity produced by its components realizing processes within the unity itself? Do all of the unity's components participate in the production of its components?

A somewhat simplified description of an "autopoietic machine" was later given by Maturana and Varela (ref. 2356, p.79) as: "a machine organized (defined as a unity) as a network of processes of production (transformation and destruction) of components that produces the components which: (i) through their interactions and transformations continuously regenerate and realize the network of processes (relations) that produced them; and (ii) constitute it (the machine) as a concrete entity in the space in which they (the components) exist by specifying the topological domain of its realization as such a network." Thus an autopoietic machine (which is self-maintaining and self-repairing, but may or may not be capable or self-replication, a very specialized ability) is composed of components which engage in a network of interactions that enable the continuous regeneration of these same components.[2373] (An "allopoietic" machine has as its product something different from itself.) Autopoiesis has been applied to communication,[1853,1856] management,[1855,1857] economics,[2374] psychology,[1854] and sociological[1850-1852] systems, as well as to biological and purely mechanistic systems.

While interesting, general philosophical discussions of autopoietic reproduction[2375-2378] and formal mathematical definitions of autopoiesis,[2386] self-replication and self-reproduction[2387-2389] are beyond the limited scope of this engineering-oriented book, as are broad discussions of general systems theory as applied to replicating systems.[2390-2396] More useful to the replicating systems engineer are specific conceptual taxonomies that may provide guidance to investigations of the replicator design space. Thus we begin our analysis by summarizing a selection of replicator and replicator-relevant artificial life taxonomies that have been described in the past, including the Dawkins classification of replicators (Section 5.1.1), the Miller critical subsystems of living systems (Section 5.1.2), the Hasslacher-Tilden MAP survival space (Section 5.1.3), the Szathmary classification of replicators (Section 5.1.4), the POE model of bio-inspired hardware systems (Section 5.1.5), the Taylor categorization of reproducers (Section 5.1.6), the Bohringer taxonomy of microassembly (Section 5.1.7), and the Suthakorn-Chirikjian categorization of self-replicating robots (Section 5.1.8). The replication models of von Neumann and others have already been reviewed at length in Chapter 2. It should be emphasized that our review is only a selection and not a comprehensive survey of all such efforts, nor is our effort a "taxonomy of taxonomies",[2399] and any systematic consideration of purely computational artificial life entities[2400,2401] or cellular automata arrays[383,2402] is specifically excluded.

Our own replicator taxonomy, presented here for the first time (Section 5.1.9), constitutes perhaps the first crude but comprehensive map of the entire kinematic replication design space, subsuming all known prior work and providing a wealth of new design dimensions that may inform and inspire future engineering design efforts. Our design space at minimum identifies $>10^{70}$ theoretical distinct kinematic replicator subclasses, confirming our intuitive suspicion that the kinematic replicator design space* is truly vast — and, as yet, largely unexplored by human engineers.

5.1.1 Dawkins Classification of Replicators (1976)

According to a brief summary by Brandon,[2403] biologist Richard Dawkins in his classic 1976 work *The Selfish Gene*[275] defines a replicator as "anything in the universe of which copies are made". Dawkins observes that three characteristics affect the quality of replicators: **fecundity**, **fidelity**, and **longevity**: "What is of evolutionary importance is that it produces copies of itself so that it is potentially immortal in the form of copies. Of course, everything else being equal, the more copies [that] are replicated (fecundity) and the more accurately a replicator produces them (fidelity), the greater its longevity and evolutionary success." In addition to these three characteristics, Dawkins offers two additional useful design dimensions in his classification of replicators.

First, replicators may be **active or passive**. An active replicator is an entity that influences its probability of being replicated — for example, any DNA molecule which, either through protein synthesis or the regulation of protein synthesis, has some phenotypic effect. On the other hand, a passive replicator is one which has no influence on its probability of being copied, such as a section of DNA that is not transcribed.

Second, replicators may be **germ-line or dead-end**, depending on whether they are potential ancestors of an indefinitely long line of descendant replicators. For instance, the gene in a gamete or germ-line cell in a body is a germ-line replicator, whereas most of the genes in our bodies are not germ line and can replicate only a finite number of times through mitosis, thus are dead-end replicators. Brandon notes that "it is the potential, not the fact, of being in an indefinitely long ancestry that matters for this classificatory distinction. So a gene in a spermatozoon that fails to fertilize is still a germ line replicator."

For living systems, evolution by natural selection is a two-step process — (1) the direct replication of structure, and (2) an interaction with the environment so that replication is differential across different entities, traditionally called phenotypes. The notion of phenotypes seems adequate for discussions of organismic selection, but entities other than organisms such as chromosomes, groups of organisms, or even entire species can interact with their environment in a way that also makes replication differential. Thus Hull[2404] suggests the more general term "interactor" as "an entity that directly interacts as a cohesive whole with its environment in such a way that replication is differential." Dawkins regards organisms necessarily as vehicles that are secondary to their replicators (i.e., their "selfish genes"), with any change in replicator structure passed on during the process of replication. But Brandon[2403] notes that "it is easy to imagine self repairing replicators where changes in structure would not necessarily be passed on in replication," a potentially useful distinction in the case of artificial mechanical replicators as opposed to gene-driven biological replicators. Brandon continues: "What seems to be important is that replication be direct and accurate. Directness and accuracy are terms of degree, and if we allow some play in both, under certain circumstances an organism could be considered a replicator." McMullin[2405] has noted additional qualifications to Dawkins' schema relating to the "units of selection" issue.

5.1.2 Miller Critical Subsystems of Living Systems (1978)

Seeking to devise a "general theory of living systems," in 1978 the late James Grier Miller[2393,2394] set forth a conceptual framework in which living systems at all size scales are defined as "open systems composed of subsystems which process inputs, throughputs, and outputs of various forms of matter, energy, and information.“ Miller identified 19 critical subsystems whose processes are deemed essential for life and which together comprise a living system. Most of the 19 subsystems are found at all hierarchical levels of living systems, running through cells, organs, organisms, groups, organizations, societies, and even supranational systems. However, not all of these subsystems are strictly essential for self-replication, so disabling or removing some of them results in a system capable of replication only in limited circumstances, which is more desirable from a commercial or public safety viewpoint.[271] (For example, an externally-controlled replicator would not need an onboard Decider subsystem.) Space does not permit more than a listing and brief description of each of the 19 critical subsystems, taken verbatim from Miller's discussion:[2393]

Subsystems which process both matter-energy and information

1. **Reproducer** — the subsystem which is capable of giving rise to other systems similar to the one it is in. This process fundamentally involves transmission of information, the template of the new system. The matter-energy which is organized to compose the new system, however, must also be processed. The care of the next generation of systems until they become independent and self-supporting is also a function of this subsystem. In all systems the reproducer operates by many complex, reversible functions, but the ultimate effect is to bring about an irreversible, historical change, the creation of the new systems of a new generation.

** The design space of virtual replicators, particularly cellular automata, appears somewhat more amenable to analysis. Some automated explorations of this design space have already begun. For example, Lohn and Reggia[383] have used a genetic algorithm to automatically design self-replicating structures in cellular automata models, which "sheds light on the process of creating self-replicating structures, which could potentially lead to future studies on the discovery of novel self-replicating molecules and self-replicating assemblers in nanotechnology." Koza[372] has pointed out that the design space of cellular automata may also be enormously vast, with the number of possible distinct 200,000-cell 29-state automata exceeding $10^{292,480}$.*

2. **Boundary** — the subsystem at the perimeter of a system that holds together the components which make up the system, protects them from environmental stresses, and excludes or permits entry to various sorts of matter-energy and information.

Subsystems which process primarily matter-energy

3. **Ingestor** — the subsystem which brings matter-energy across the system boundary from the environment.
4. **Distributor** — the subsystem which carries inputs from outside the system or outputs from its subsystems around the system to each component.
5. **Converter** — the subsystem which changes certain inputs to the system into forms more useful for the special processes of that particular system.
6. **Producer** — the subsystem which forms stable associations that endure for significant periods among matter-energy inputs to the system or outputs from its converter, the materials synthesized being for growth, damage repair, or replacement of components of the system, or for providing energy for moving or constituting the system's outputs of products or information markers to its suprasystem.
7. **Matter-Energy Storage** — the subsystem which retains in the system, for different periods of time, deposits of various sorts of matter-energy.
8. **Extruder** — the subsystem which transmits matter-energy out of the system in the forms of products or wastes.
9. **Motor** — the subsystem which moves the system or parts of it in relation to part or all of its environment, or moves components of its environment in relation to each other.
10. **Supporter** — the subsystem which maintains the proper spatial relationships among components of the system, so that they can interact without weighting each other down or crowding each other.

Subsystems which process primarily information

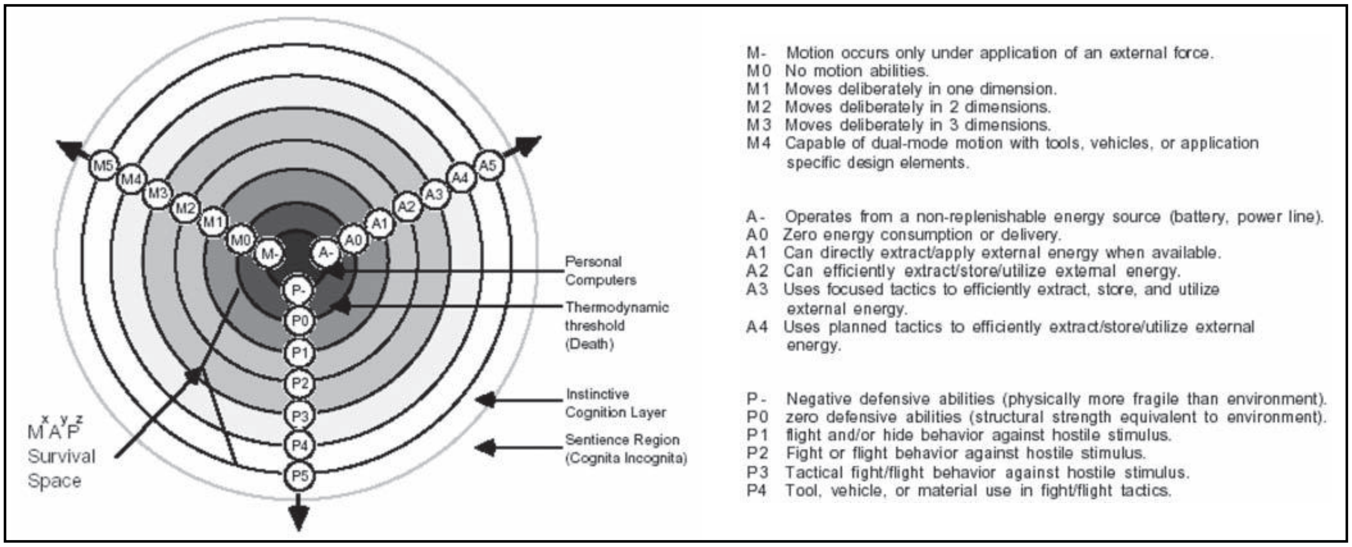
11. **Input Transducer** — the sensory subsystem which brings markers bearing information into the system, changing them to other matter-energy forms suitable for transmission within it.
12. **Internal Transducer** — the sensory subsystem which receives, from subsystems or components within the system, markers bearing information about significant alterations in those subsystems or components, changing them to other matter-energy forms of a sort which can be transmitted within it.
13. **Channel and Net** — the subsystem composed of a single route in physical space, or multiple interconnected routes, by which markers bearing information are transmitted to all parts of the system.
14. **Decoder** — the subsystem which alters the code of information input to it through the input transducer or internal transducer into a "private" code that can be used internally by the system.
15. **Associator** — the subsystem which carries out the first stage of the learning process, forming enduring associations among items of information in the system.
16. **Memory** — the subsystem which carries out the second stage of the learning process, storing various sorts of information in the system for different periods of time.
17. **Decider** — the executive subsystem which receives information inputs from all other subsystems and transmits to them information outputs that control the entire system.
18. **Encoder** — the subsystem which alters the code of information input to it from other information processing subsystems, from a "private" code used internally by the system into a "public" code which can be interpreted by other systems in its environment.
19. **Output Transducer** — the subsystem which puts out markers bearing information from the system, changing markers within the system into other matter-energy forms which can be transmitted over channels in the system's environment.

5.1.3 Hasslacher-Tilden MAP Survival Space (1994-1995)

Brosl Hasslacher and Mark W. Tilden at Los Alamos National Laboratory have devised[185] a robotics design space for the creation of machines whose functions are intended to "guarantee an autonomous machine's survival," based on the following set of "biomorphic survival laws":

1. a machine must protect its existence;
2. a machine must acquire more energy than it exerts; and
3. a machine must exhibit (directed) motion.

These requirements define the Mobility, Acquisition, and Protection (MAP) survival space for autonomous biomorphic designs shown in Figure 5.1. The authors claim that full autonomous



M5
M4
M3
M2
M1
M0
M-
A-
A0
A1
A2
A3
A4
A5
P-
P0
P1
P2
P3
P4
P5
Personal Computers
Thermodynamic threshold (Death)
Instinctive Cognition Layer
Sentience Region (Cognita Incognita)
$M^{x}A^{y}P^{z}$ Survival Space

M-	Motion occurs only under application of an external force.
M0	No motion abilities.
M1	Moves deliberately in one dimension.
M2	Moves deliberately in 2 dimensions.
M3	Moves deliberately in 3 dimensions.
M4	Capable of dual-mode motion with tools, vehicles, or application specific design elements.
A-	Operates from a non-replenishable energy source (battery, power line).
A0	Zero energy consumption or delivery.
A1	Can directly extract/apply external energy when available.
A2	Can efficiently extract/store/utilize external energy.
A3	Uses focused tactics to efficiently extract, store, and utilize external energy.
A4	Uses planned tactics to efficiently extract/store/utilize external energy.
P-	Negative defensive abilities (physically more fragile than environment).
P0	zero defensive abilities (structural strength equivalent to environment).
P1	flight and/or hide behavior against hostile stimulus.
P2	Fight or flight behavior against hostile stimulus.
P3	Tactical fight/flight behavior against hostile stimulus.
P4	Tool, vehicle, or material use in fight/flight tactics.

Figure 5.1. The complete MAP survival space. (courtesy of Hasslacher and Tilden[185])

operation of artificial "biomorphs" requires sensation, cognition, locomotion, and manipulation, though it is possible for machines to survive on locomotion alone. Clearly several additional capabilities would be required for these machines to exhibit self-replication as well as mere survival (durability), but the authors do not discuss this possibility.

Hasslacher and Tilden evidently believe that machine replication is both difficult and undesirable, and thus recommend instead building robots that are extremely durable: "Machines cannot be made to reproduce themselves easily, nor would we want them to. At small scales, with carbon-based materials platforms, self-reproduction could be quite dangerous. Therefore if machines are to survive acceptably then we must extend their lifetime to many years in full operation. This means an autonomous machine must extract power from its environment and since that power may be either weak or scarce, it must be able to operate by storage of and access to power on demand. In normal scale environments this implies solar powered machines."

In the case of micron-scale machines fabricated using silicon-based lithography: "At this scale self-assembling colonies of biomorphic machines are not only practical, but desirable. Colonies should both self-organize physically and develop collective or emergent behavior....A colony of diverse biomorphic tiles could create a space of finite elements that organize into larger collective creatures with a potential for tile-cluster 'reproduction'. That is, there may be tile structures that make copies of themselves from the suspended tile matrix they 'live' in, ...[which] would lead to observed machine reproduction in a safe, linear regime, rather than dangerous exponential growth." However, no details are given as to how the individual micron-scale machines or "biomorphic tiles" might assist in the fabrication of additional similar such machines.

Some research on biologically-inspired microscale robots has begun.[2406-2410]

5.1.4 Szathmary Classification of Replicators (1995-2000)

Starting in 1995 originally in collaboration with John Maynard Smith,[2415] and continuing through a succession of refinements over several years,[2411-2417] Eors Szathmary has created an interesting classification of replicators which identifies five distinct bi-valued properties of replicators, as follows:

Potential: *Limited Heredity* **or** *Unlimited Heredity*
Mode: *Holistic* **or** *Modular*
Level: *Phenotypic* **or** *Genotypic*
Set: *Solitary* **or** *Ensemble*
Maintenance: *Attractor-based* **or** *Storage-based*

1. **Potential**. Like Dawkins,[275] Szathmary[2415] in 1995 originally distinguished replicators having *limited heredity* and potentially *unlimited heredity*. Replicators with potentially unlimited heredity can have many more types than the number of objects in any realistic system, whereas replicators with limited heredity have fewer or only about the same number of types than the number of objects in realistic systems — that is, they "exist only in a few alternate types," or, possibly, only in a single type. "Systems with limited heredity have only a limited evolutionary potential because the number of available types is too low."[2417] Pattee[2418] also recognized the importance of "hereditary process" in reproduction.
2. **Mode**. Szathmary[2415] also originally distinguished replicators according to their mode of synthesis, of which there are two types. In the first mode of synthesis, originally termed *processive*[2415] and later *holistic*,[2416,2417] the information carried is of an analog character and the process passes through a continuum of closely-related states, most nearly resembling an autocatalytic chemical reaction or a cyclically processive reaction like the citric acid cycle, or the "replication" demonstrated by spreading fire or even by a series of falling dominoes. "Chemical cycles, such as the formose reaction,[2419] are holistic replicators since replication is not based on the successive addition of modules."[2417] In the second mode of synthesis, termed *modular*,[2412,2415-2417] the information carried is of a digital[*] character[2420] and the process passes through a series of discrete states, as exemplified by the complementary-shape interactions observed in DNA. For example, oligonucleotides are copied by the template effect of a sequence composed of digits (modules) belonging to a restricted alphabet.[2412] A large number of artificial oligonucleotide modular replicators are now known.[1361-1367,1373]
3. **Level**. In 1999, Szathmary[2416] revised his classification of replicators to include a new functional dimension based on the level at which replication takes place — either *phenotypic* or *genotypic*. In phenotypic replicators, the phenotype (physical structure) of the replicator is transmitted without genotype (structure description) copying. Replication occurs without needing an onboard instruction tape (the genotype) to be copied along with the physical structure of the replicator. "Phenotypic replicators do not pass on their genotypes, only some aspects of the phenotype are transmitted. Phenotypic replicators with limited heredity include genetic membranes,[2422] prions[2423-2425] and simple memetic systems."[2417] Cortical inheritance in ciliates[2426] is another phenotypic inheritance system "whereby the orientation of kinetids (basal body plus associated cortical and fibrillar structures) is passed on from cell generation to generation."[2416] Still another example of a phenotypic replicator, having unlimited heredity, would be Laing's example (Section 2.3.5) of machine replication by inspection. By contrast, in genotypic replicators, phenotype duplication requires duplicating the genotype along with the replicator structure.
4. **Set**. In 2000, Szathmary[2417] further distinguished replicators according to the set of entities capable of replication. In *solitary* replication, each member of a set of entities is individually capable of replication. In *ensemble* replication, no individual entity is individually capable of replication and only the set as a whole can replicate. "Replicator networks consisting of catalytic molecules (such as reflexively autocatalytic sets of proteins,[1626,1662,2396-2398] or self-reproducing lipid vesicles[2427,2428]) are hypothetical ensemble replicators. Ensemble replicators suffer from the paradox of specificity: while their abstract feasibility seems to require a high number of molecular types, the harmful effect of side reactions calls for a small system size."[2417]
5. **Maintenance**. Also in 2000, Szathmary[2417] added the concept of *attractor-based* heredity to his replicator classification scheme, in which goal maintenance of the replicating systems is achieved either by stochastic gravitation toward an "attractor" in the dynamic control space, or more directly by "storage" based control information. For example, the membrane vesicle can be

---

[*] *In 2002, Ellington and Levy[2421] proposed a similar replicator nomenclature in which nucleic acid and peptide replicators are considered either "digital" ("composed of discrete units...that can alternate between stable states, [and] can be combined into an informational code") or "continuous" ("capable of giving rise to a variety of products"). Note the authors: "The structural complementarity of discrete replicators is of necessity greater than that of other replicators. However, increased complementarity leads to product inhibition. These facts imply a fundamental conundrum: the less discrete a replicator is, the less information it can transfer; the more discrete a replicator is, the more its evolution is limited by parabolic growth."*

considered a molecular replicator[1333] and this system is attractor-based[2429] "since it is the dynamical nature of the network of reactions that makes replication possible, and the identity of the network is preserved by its dynamical stability (the system's basin of attraction)".[2417] Attractor-based systems can have limited heredity only.* [2417] In contrast, information carried by gene-like replicators is *storage-based*:[2429] "to a good approximation all possible gene sequences are equally stable and transmissible, using the same copying mechanism".[2417] Storage-based systems (e.g., contemporary DNA-based organisms) can have unlimited hereditary potential.[2417] Szathmary[2417] also notes that "the typical path of evolution goes from limited to unlimited heredity, and from attractor-based [and holistic] to modular (digital) replicators."

5.1.5 Sipper POE Model of Bio-Inspired Hardware Systems (1997)

Moshe Sipper and colleagues[384,535,2430-2434] have devised a simple classification scheme for artificial life (ALife) systems that may be useful for some classes of artificial replicators as well. In the authors' words: "Living organisms are complex systems exhibiting a range of desirable characteristics, such as evolution, adaptation, and fault tolerance, that have proved difficult to realize using traditional engineering methodologies. Recently, engineers have been allured by certain natural processes, giving birth to such domains as artificial neural networks and evolutionary computation. If one considers life on Earth since its very beginning, then the following three levels of organization can be distinguished."

1. **Phylogeny**. "The first level concerns the temporal evolution of the genetic program, the hallmark of which is the evolution of species, or phylogeny. The multiplication of living organisms is based upon the reproduction of the program, subject to an extremely low error rate at the individual level, so as to ensure that the identity of the offspring remains practically unchanged. Mutation (asexual reproduction) or mutation along with recombination (sexual reproduction) give rise to the emergence of new organisms. The phylogenetic mechanisms are fundamentally non-deterministic, with the mutation and recombination rate providing a major source of diversity. This diversity is indispensable for the survival of living species, for their continuous adaptation to a changing environment, and for the appearance of new species."
2. **Ontogeny**. "Upon the appearance of multicellular organisms, a second level of biological organization manifests itself. The successive divisions of the mother cell, the zygote, with each newly formed cell possessing a copy of the original genome, is followed by a specialization of the daughter cells in accordance with their surroundings, i.e., their position within the ensemble. This latter phase is known as cellular differentiation. Ontogeny is thus the developmental process of a multicellular organism. This process is essentially deterministic: an error in a single base within the genome can provoke an ontogenetic sequence which results in notable, possibly lethal, malformations."
3. **Epigenesis**. "The ontogenetic program is limited in the amount of information that can be stored, thereby rendering the complete specification of the organism impossible. A well-known example is that of the human brain with some 10^{10} neurons and 10^{14} connections, far too large a number to be completely specified in the four-character genome of length approximately 3 x 10^9. Therefore, upon reaching a certain level of complexity, there must emerge a different process that permits the individual to integrate the vast quantity of interactions with the outside world. This process is known as epigenesis, and primarily includes the nervous system, the immune system, and the endocrine system. These systems are characterized by the possession of a basic structure that is entirely defined by the genome (the innate part), which is then subjected to modification through lifetime interactions of the individual with the environment (the acquired part). The epigenetic processes can be loosely grouped under the heading of learning systems."

By analogy to nature, the design space of bio-inspired hardware systems can be partitioned along the three axes of phylogeny, ontogeny, and epigenesis (the POE model;[2430-2432] Figure 5.2) with the axes defined as follows: the phylogenetic axis involves evolution; the ontogenetic axis involves the development of a single individual from its own genetic material, essentially without environmental interactions; and the epigenetic axis involves learning through environmental interactions that take place after formation of the individual.

For example,[2433] hardware implementations of the following three paradigms can be positioned along the POE axes as follows: (1) evolutionary algorithms are the simplified artificial counterpart of phylogeny ("P" axis") in nature; (2) multicellular automata are based on the concept of ontogeny ("O" axis), where a single mother cell gives rise, through multiple divisions, to a multicellular organism; and (3) artificial neural networks embody the epigenetic process ("E" axis), where the system's synaptic weights and perhaps topological structure change through interactions with the environment.

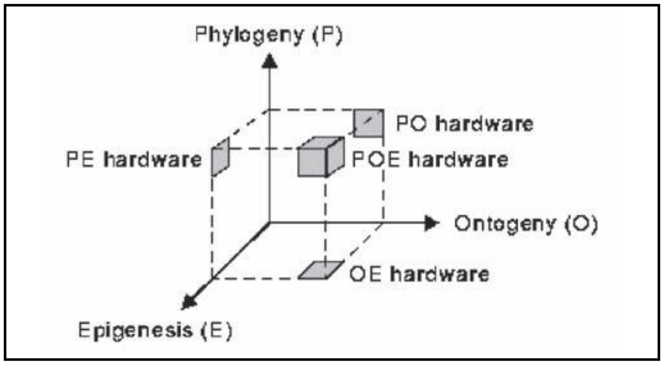


Figure 5.2. The POE taxonomy of bio-inspired systems.[2433] Combining POE axes in order to create novel bio-inspired systems: The PO plane involves evolving hardware that exhibits ontogenetic characteristics, such as growth, replication, and regeneration. The PE plane includes, e.g., evolutionary artificial neural networks. The OE plane combines ontogenetic mechanisms (self-replication, self-repair) with epigenetic (e.g., neural network) learning. The POE space comprises systems that exhibit characteristics pertaining to all three axes, such as an artificial neural network (epigenetic axis), implemented on a self-replicating multicellular automaton (ontogenetic axis), whose genome is subject to evolution (phylogenetic axis). (courtesy of Moshe Sipper)

** C. Phoenix[572] observes that the set of attractors stabilizes the system but is also defined by the system. There is no requirement that offspring have the same attractor-configuration as their parents. If offspring can explore an attractor-space capable of containing several attractor-configurations, then heredity could be unlimited.*

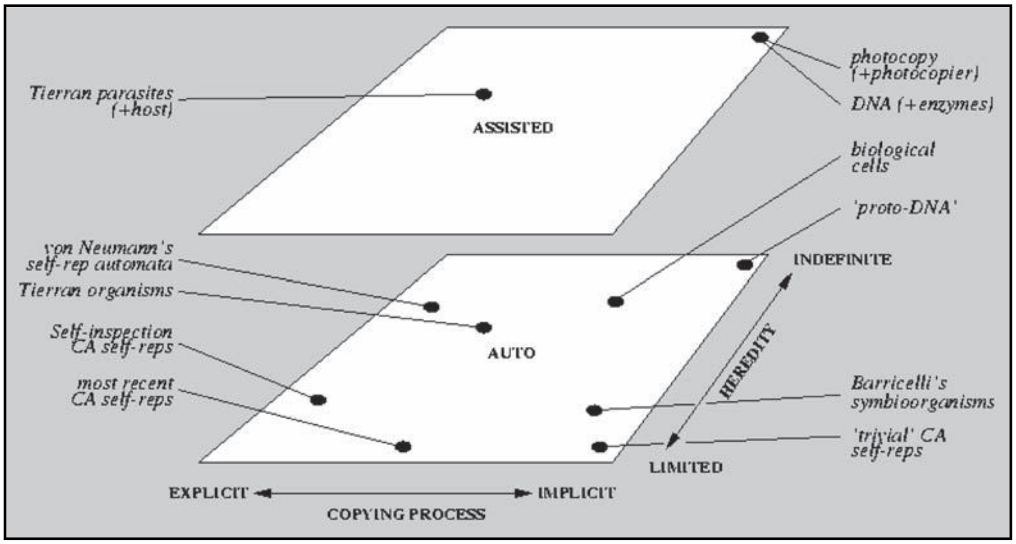


Figure 5.3. Taylor's "Categorization of Reproducers".[444] (courtesy of Tim Taylor)

5.1.6 *Taylor Categorization of Reproducers (1999)*

In his 1999 Ph.D. thesis on artificial life, Tim Taylor[444] focuses on three important dimensions defining the replication design space:

1. **Explicit-Implicit Coding** scale — the degree to which the algorithm for reproduction (the way in which the process is specified and controlled) is *explicitly encoded* on the configuration being reproduced, rather than being *implicit in the physical laws* of the world. This distinction defines a continuum of possibilities.
2. **Auto-Assisted Reproduction** scale — whether reproduction happens purely by the action of the physical laws of the world on the configuration to be reproduced (*auto*-reproduction), or whether it also requires auxiliary physical (or logical) machinery (*assisted*-reproduction). Taylor suggests that this distinction defines only a dichotomy, but allowing varying degrees of "assistance" would produce a continuum along this design dimension as well.
3. **Limited-Indefinite Hereditary** scale — the number of different configurations that exist, connected by mutational pathways, that are capable of reproducing their specific form — that is, the distinction between *limited hereditary* reproducers and *indefinite hereditary* reproducers, a distinction also cited by Dawkins (Section 5.1.1) and Szathmary (Section 5.1.3). This factor could be expressed as the proportion of all possible mutations the reproducer may experience that will result in the production of distinct, yet viable, reproducers. This distinction also defines a continuum of possibilities, and indeed this axis may be infinitely long.

Taylor notes that these three scales seem "generally independent of each other" — i.e., they are mutually orthogonal dimensions in the design space — although he admits "the more explicitly encoded the reproduction algorithm is, the less likely, in general, it is to be an indefinite hereditary reproducer because of the increased chance of mutations disrupting the copying process." Figure 5.3 shows Taylor's qualitative categorization of some well-known replicating systems.

Taylor[444] notes that in his schema, Tierran organisms (Section 2.2.1) and von Neumann's self-reproducing cellular automata (Section 2.1.3) "are placed midway along the limited-indefinite hereditary scale because, although both representations are capable of supporting universal computation in principle, only mutations which retain the ability to reproduce will be viable. In particular, in von Neumann's architecture a mutation which affects a section of the tape which encodes the constructing automaton, the copying automaton or the control automaton will generally disrupt the ability of the combined automaton to produce viable offspring. Likewise, in Tierra a mutation which affects a section of the program which encodes the self-reproduction algorithm will generally disrupt the ability of the program to reproduce."

Taylor[444] classifies DNA reproduction as assisted, because DNA can replicate "only with the aid of a host of enzymes to control the unwinding of the double helical structure, the polymerization of the individual bases of the new molecule, etc. At the same time, DNA is, in the presence of suitable enzymes, capable of indefinite heredity assisted-reproduction; the enzymes are able to copy any DNA double helix, no matter what sequence of bases it comprises. Within this context, the copying process is implicitly encoded in the DNA's environment (in the enzymes which support the reproduction process, and in the physical laws governing the inherent bonding affinities of the bases) rather than being explicitly encoded upon individual strands on DNA. In contrast, a cell as a whole can be considered an auto-reproducer, as it can completely direct its own reproduction (in the presence of sufficient energy and raw materials from the environment), but its hereditary potential is slightly more restricted than DNA assisted-reproduction, because some mutations may disrupt the ability of the cell to reproduce. Similarly, each of Barricelli's symbioorganisms (Section 2.2.1) can be considered, collectively, as an auto-reproducer, although individual digits within the symbioorganism are assisted-reproducers. The same analysis can be applied to collectively-autocatalytic reaction networks (e.g., Kauffman[2396])."

The hypothetical 'proto-DNA' (i.e., a desirable seed for open-ended evolution) is placed in the auto-implicit-indefinite hereditary corner of the space because "the seed should be auto-reproducing (i.e., not rely upon auxiliary machinery) if it is to have a reasonable chance of spontaneously emerging, and it should be an indefinite hereditary reproducer to support an ongoing, open-ended evolutionary process. The requirement that it be an indefinite hereditary reproducer is most easily fulfilled if it reproduces implicitly."

5.1.7 *Bohringer et al Taxonomy of Microassembly (1999)*

Bohringer, Fearing, and Goldberg[2435] presented in 1999 a preliminary summary of techniques then in use for microscale assembly:

1. **Serial Microassembly** — parts are put together one by one according to the traditional pick-and-place paradigm, including the following techniques:
   A. Manual assembly with tweezers and microscopes.
   B. Visually based and teleoperated microassembly.[2241,2436,2437]

   C. High-precision macroscopic robots: stepping motors and inertial drives are used for submicron motion resolution[2438-2440] or MRSI assembly robots[2441] for surface-mount electronics components of submillimeter size.
   D. Microgrippers with gripper sizes of 100 microns or less.[2442-2445]
2. **Deterministic Parallel Microassembly** — multiple parts of identical or different design are assembled simultaneously, wherein the relationship between a part and its destination is known in advance, including the following techniques:
   A. Flip-chip wafer-to-wafer transfer: a wafer with partially released components is carefully aligned and pressed against another substrate. When the wafers are separated again, the components remain bonded to the second substrate.[1152,2449]
   B. Microgripper arrays capable of massively parallel pick-and-place operations.[2444]
3. **Stochastic Parallel Microassembly** — multiple parts of identical or different design are assembled simultaneously, wherein the relationship between the part and its destination is unknown or random. The parts "self-assemble" during stochastic processes, in analogy to annealing, using the following effects as motive forces:
   A. Fluidic agitation and mating part shapes.[1326,2450]
   B. Vibratory agitation and electrostatic force fields.[1338-1341]
   C. Vibratory agitation and mating part shapes.[1552]
   D. Mating patterns of self-assembling monolayers.[2435]

5.1.8 Suthakorn-Chirikjian Categorization of Self-Replicating Robots (2002-2003)

Gregory Chirikjian and Jackrit Suthakorn, a graduate student in Chirikjian's group at Johns Hopkins University, have pursued an active research program on macroscale kinematic self-replicating systems (Section 3.23). The group settled on a simple, pragmatic operational definition[1284-1286] of self-replication as "the process of assembling a functional robot from passive components — the robot that is assembled (the replica) is an exact copy of the robot doing the assembling." Suthakorn's categorization of self-replicating robots (Figure 5.4) makes a primary distinction according to their behavior: **Directly Replicating** (a robot capable of producing an exact replica of itself in one generation) and **Indirectly Replicating** (a robot capable of producing one or more intermediate robots that are in turn capable of producing replicas of the original).[1284-1287]

Directly Replicating robots are classified into four subgroups depending on the characteristics of their self-replication processes. These four subgroups are described by Suthakorn[1284-1287] as follows:

1. **Fixture-Based Replication**. Robots in this group depend on external fixtures (ranging from simple hooks to complex structures for restraining delicate parts during assembly) to complete the self-replication process (Figures 3.72 and 3.74). Some subsystems may require high precision positioning for assembling parts. Passive fixtures can assist in this because of the shape constraints that they impose, and push-pull fixtures are helpful as well. Fixtures serve as a substrate or catalyst to assist in the self-replication process, but are themselves not actuated.
2. **Operating-Subsystem-in-Process Replication**. In this group, one or several subsystems of the replica can operate before the replica itself is fully assembled. These subsystems can then assist the original robot during its assembly of its replica (Figure 3.75). This assistance can come in many forms — for instance, with functioning subsystems helping to align, manipulate, or transport parts.
3. **Single-Robot-without-Fixture Replication**. In this group, a single robot finishes the self-replication process and depends only on the available environment (Figure 3.73). The complexity of the subsystems or the number of subsystems in the replica is usually very low for this experimental group because without fixtures or multiple cooperating robots, it is more difficult to position large numbers of subsystems with the requisite high precision to achieve successful replication. (This does not challenge the idea of a self-contained molecular assembler because a robot can have fixtures integral to it, and because if the subsystems are of sufficiently low complexity (i.e., atoms) the robot can incorporate large numbers of them.)
4. **Multi-Robot-without-Fixture Replication**. In this group, multiple robots work together in the self-replication process without the assistance of fixtures. A major advantage is the reduction of the time required for self replication because different stages can be completed in parallel. A disadvantage is that there may be interference problems among robots, requiring robots to possess a greater awareness of their surroundings. Another disadvantage is that multiple robots require multiple replicas to be produced.

Indirectly Replicating robots have as their primary characteristic that the original robot or group of robots must work together to build a robot-producing factory or some type of intermediate robot

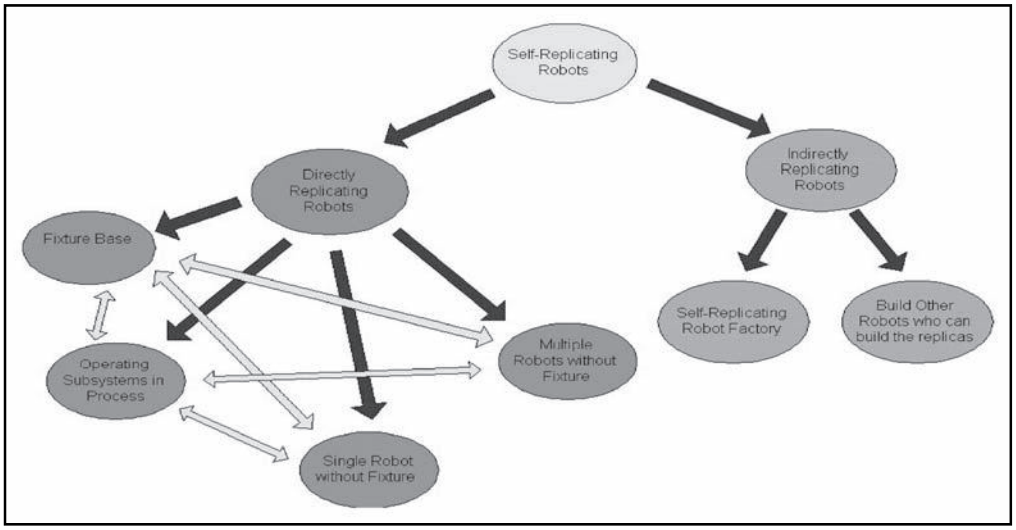

Self-Replicating Robots
Directly Replicating Robots
Indirectly Replicating Robots
Fixture Base
Operating Subsystems in Process
Single Robot without Fixture
Multiple Robots without Fixture
Self-Replicating Robot Factory
Build Other Robots who can build the replicas

Figure 5.4. Block diagram of the Suthakorn-Chirikjian categorization of self-replicating robots.[1284-1287] (courtesy of Chirikjian group, JHU)

or robots, which are subsequently able to produce replicas of the original robots or assist the original robot in replicating. In this category the original robots lack the ability to directly assemble copies of themselves. Indirectly Replicating robots may be classified into two subgroups, described by Suthakorn[1284-1287] as follows:

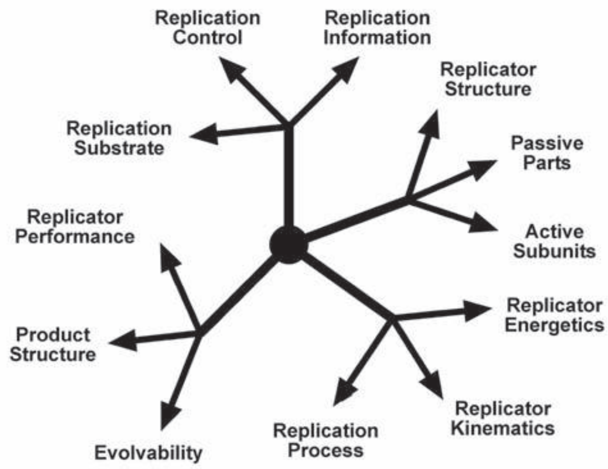
1. **Intermediate Robot Replication**. In this group, the original robot works alone or with other robots, with or without passive fixtures, to fabricate an intermediate robot or robots. The intermediates have the ability to fabricate, or assist in fabricating, replicas of the original robot that the original robot does not possess.
2. **Self-Replicating Factory**. Here the original robot works independently or in a group to construct a factory consisting of automated workcells that can then manufacture replicas of the original robot. This differs from intermediate robots and passive fixtures because workcells are fixed automation elements that can be fully actuated.

5.1.9 Freitas-Merkle Map of the Kinematic Replicator Design Space (2003-2004)

Taking the broadest possible view, a manufacturing system is a physical system that can make other physical systems. Manufacturing systems potentially can only make either (or both) of two kinds of things: (1) self (another manufacturing system), or (2) non-self products. A kinematic replicator is an example of a manufacturing system. More specifically, a kinematic replicator is a manufacturing system that can make an architecturally identical copy of itself. This logically defines three broad classes of manufacturing systems:

1. **Productive Nonreplicators** — manufacturing systems that can only make non-self products. These systems cannot make copies of themselves and are not replicators. This class of manufacturing system represents essentially all of today's factory/distribution-centered industrial machinery, and may also characterize early nanoscale- or nanostructure-manufacturing product lines, whether employing self-assembly or positional assembly processes (Chapter 4), as well as future highly specialized nanomanufacturing systems.
2. **Nonproductive Replicators** — manufacturing systems that can only make copies of themselves. These purely parasitic systems are inherently useless from a societal or commercial standpoint, and should in most cases prove brittle when the environment (in which replication must occur) changes. Viruses are an example of nonproductive replicators in biology.
3. **Productive Replicators** — manufacturing systems that can make copies of themselves and can also make non-self products. These are the factory systems of the future. As Bradley (Section 3.12) has already noted, the process of replication in most cases will use only "a vanishingly small fraction of total capabilities" of a replicator — that is, most of the practical operational space of a replicator is likely to be the ability to manufacture non-self products.

The ability of productive replicators to make both self and non-self products — one basic measure of replicator performance — constitutes but a single dimension (i.e., J6 on our map) within an enormously vast multidimensional replicator engineering design space. The distinction between individual and factory replicators is another dimension (I4) in the space. We have identified 137 practical multivalued replicator design properties which may be grouped into 12 primary design dimensions in four principal categories (Figure 5.5):



A. REPLICATION CONTROL
A1. Replication Control Autonomy
A2. Replication Control Redundancy
A3. Replication Control Centralization
A4. Replication Control Abstractivity
A5. Replication Control Source
A6. Replication Control Complexity
A7. Replication Control Maintenance
A8. External Veto Authority
A9. Embedded Replication Veto

B. REPLICATION INFORMATION
B1. Replication Information Autonomy
B2. Replicator Information Redundancy
B3. Replicator Information Centralization
B4. Replication Information Abstractivity
B5. Replication Information Type
B6. Replicator Description Size
B7. Replication Information Sharing
B8. Replicator Information Lockout
B9. Replicator Description Alphabet
B10. Replicator Triviality or Complexity
B11. Replicator Pattern Instantiation Specificity
B12. Replicator Information Context Tolerance

C. REPLICATION SUBSTRATE
C1. Substrate Physicality
C2. Substrate Naturalicity
C3. Substrate Technology Level
C4. Substrate Physical Dimensionality
C5. Replication Substrate Phase
C6. Replication Substrate Temperature
C7. Substrate Sufficiency
C8. Environmental Fixture Requirement
C9. Feedstock Import through Boundary
C10. Entropy of Substrate
C11. Self-Replicability
C12. Fixture Acquisition

D. REPLICATOR STRUCTURE
D1. Replicator Physicality
D2. Replicator Naturalicity
D3. Replicator Technology Level
D4. Replicator Physical Dimensionality
D5. Replicator Scale
D6. Replicator Mass
D7. Replicator Boundary
D8. Product Export through Boundary
D9. Replicator Structural Fixity
D10. Replicator Particity
D11. Process Materials Storage
D12. Replicator Computer
D13. Replicator Continguity

E. PASSIVE PARTS
E1. Passive Constituent Parts Count
E2. Passive Constituents Parts Scale
E3. Passive Constituent Parts Types
E4. Number of Vitamin Parts
E5. Replicator Nutritional Complexity
E6. Required Parts Preparation
E7. Passive Parts Complexity
E8. Parts Precision
E9. Multiple Utility of Passive Parts
E10. Parts Presentation
E11. Mode of Dimensional Specification

F. ACTIVE SUBUNITS
F1. Multicellularity
F2. Active Subunits Scale
F3. Active Subunits Types
F4. Active Subunits Complexity
F5. Subunit Fate
F6. Subunit Targeting
F7. Multiple Utility of Active Subunits
F8. Subunits Presentation
F9. Process Functionality of Active Subunits
F10. Timing of Subunit Activation

G. REPLICATOR ENERGETICS
G1. Process Energy Autonomy
G2. Process Energy Redundancy
G3. Process Energy Centralization
G4. Number of Onboard Process Energy Types
G5. Process Energy Types
G6. Process Energy Storage
G7. Process Energy Efficiency
G8. Replicative Energy Commitment

H. REPLICATOR KINEMATICS
H1. Process Manipulation Autonomy
H2. Process Manipulation Redundancy
H3. Process Manipulator Centralization
H4. Number of Manipulator Types
H5. Replicator Manipulation Degrees of Freedom
H6. Assembly Mechanism Style
H7. Positional Accuracy

J. REPLICATOR PERFORMANCE
J1. Replication Time
J2. Replicator Longevity
J3. Replicator Expiration Date
J4. Generational and Gestational Fecundity
J5. Generational Longevity
J6. Nonreplicator Product Types
J7. Qualitative/Quantitative Closure
J8. Emission of Waste Products

I. REPLICATION PROCESS
I1. Replicative Influence
I2. Replicator Activity/Passivity
I3. Replicator Parasiticity
I4. Replication Process Centralization
I5. Replication Process Specialization
I6. Replication Process Timing
I7. Replication Goal Specialization
I8. Replication Process Subunit Assistance
I9. Replicator Parentage
I10. Replication Process Intermediaries
I11. Replication Auxeticity
I12. Self-Formation Modality
I13. Replication Process Parallelicity
I14. Replication Process Digitality
I15. Replicator Parts Synthesis
I16. Distinct Onboard Transformative Processes
I17. Ingestor Modality
I18. Assembly Process Style
I19. Network Connectivity
I20. Audit Trails
I21. Process Accounting
I22. Process Security
I23. Tamper Resistance
I24. Reliability of Manufacturing Operations
I25. Error Correction Mechanisms
I26. Offspring Separability

K. PRODUCT STRUCTURE
K1. Product Physicality
K2. Product Naturalicity
K3. Product Technology Level
K4. Product Physical Dimensionality
K5. Product Scale
K6. Product Mass
K7. Product Structural Fixity
K8. Product Particity
K9. Product Structural Error Rate

L. EVOLVABILITY
L1. Gendericity
L2. Offspring Fertility
L3. Number of Fertile Mutant Configurations
L4. Replication Fidelity
L5. Genomic Redundancy
L6. Environmental Partitioning
L7. Complexification
L8. Heterochrony
L9. Programmability and Learning
L10. Mode of Genomic Heritability
L11. Multilevel Genomic Heritability
L12. Interreplicator Information Transfer

Figure 5.5. The multidimensional Freitas-Merkle kinematic replicator design space.

Inputs: (A) Replication Control, (B) Replication Information, (C) Replication Substrate
Structure: (D) Replicator Structure, (E) Passive Parts, (F) Active Subunits
Function: (G) Replicator Energetics, (H) Replicator Kinematics, (I) Replication Process
Outputs: (J) Replicator Performance, (K) Product Structure, (L) Evolvability

While many of these dimensions are independent, some are quite strongly interdependent and other dimensions identify characteristics of replicators which are useful but might not be necessary in all designs. Nevertheless, each item captures an important and distinct aspect of replicator design and performance.

The basic replication model followed here is that of a physical replicator device that uses external resources (called the "substrate" or "environment", which may provide energy inputs and raw materials feedstock) to make a daughter device, and possibly also to make non-replicator products. Each of the practical design properties (which may be interdependent or mutually exclusive) that define our 137-dimensional replicator design space are briefly identified below. Our design space at minimum identifies $>10^{70}$ theoretical distinct replicator subclasses. Clearly the design space for kinematic replicators, as detailed below, is truly vast and has only been lightly explored via systematic engineering efforts to date.

A. Replication Control

A1. Replication Control Autonomy. Teleoperation corresponds to the well-known "broadcast architecture"[208-210] (Sections 2.3.6 and 4.11.3.3) — a generic term for a replicating system where the replicating units do not carry blueprints (i.e., no DNA, no assembly instructions, etc). Instead, instructions are broadcast to all replicating units which then carry out the broadcast instructions. Living systems, because they carry their own blueprints in every cell, are not using a broadcast architecture. However, within the biological cell, the ribosome is the principal protein manufacturing system — and proteins receive their operating instructions as chemical broadcast signals (mRNA messenger molecules) emitted from a central location, the cell nucleus. Block the mRNA chemical broadcast from reaching the ribosomes, and cellular protein production stops and the cell ceases replicating. The literature gives many examples of such anti-mRNA molecules being prepared experimentally for just this purpose — for example, one paper[2451] reports using a particular anti-mRNA to attack a single type of mRNA molecule, inhibiting synthesis of one particular protein by 98%. The "inherent safety" (Section 5.11) of the broadcast architecture (or the vitamin architecture) derives from the fact that the replicator can be physically separated from some vital resource (e.g., information or vitamin parts), and *not* from the fact that the system is, or is not, "biological".

Unoperated (no intelligent control)
Teleoperation (full offboard control)
Semi-Autonomous (discrete instruction block transmitted from offboard source, then executed onboard before next block is received)
Autonomous (full onboard control)

A2. Replication Control Redundancy. In the case where there is more than one source of control of a replicator, can any one source exert exclusive and complete control, or must the various sources of control either cooperate to control the whole or alternatively control only some subset of replicator activities?

Any source of control can, by itself, control whole
Only a few sources of control, each by itself, can control whole
No source of control, acting by itself, can control whole (some/all sources must cooperate to achieve control of whole)

A3. Replication Control Centralization. Muscle cells with multiple nuclei are an example of replicators having multiple sources of control. Local control systems are more lifelike, scalable, robust and adaptable than single-source or centralized control systems.[481] To enhance the prospects for "inherently safe" systems (Section 5.11), single-source or centralized control systems are probably preferred for artificial replicators. This dimension is concerned with the number of control sources a replicator possesses, as distinguished from A1 which is concerned with the location of those sources of control (onboard or offboard).

No source of active control
Single source of active control (highly centralized control)
Multiple sources of active control
Many/all subunits exert active control (highly decentralized control)

A4. Replication Control Abstractivity. How concrete, or abstract, are the instructions provided to the replicator that cause it to perform kinematic actions leading to replication or other manufacturing? In general, replicator safety should be enhanced by using less-abstract control instructions.

Control instructions specify all incremental kinematic actions performed by the replicator
Control instructions specify subroutines consisting of short series of predefined kinematic actions
Control instructions specify only high-level actions, eliciting conditional activation of one or more sets of predefined subroutines of predefined kinematic actions
No control instructions are provided (also includes cases where Brownian motion and/or self-assembly perform some low-level operations)

A5. Replication Control Source. To what degree is human control a part of the replicative process, as opposed to automatic (computer) control? Asks Evan Malone:[1166] "Hybrid systems consisting of machines and humans together are already self-replicating: technological civilizations are self-replicating, and are, in some sense, engineered. Would a factory in which humans performed operations which are commanded by an AI be more or less self-replicating than a factory in which humans command operations performed by robots?"

Automated (replication is fully automatic, entirely controlled by computer, no human in the loop)
Semiautomated (replication is partially automatic, with computer providing instruction sequences and humans providing only supervisory control)
Computer-Assisted (replication directly controlled by humans who trigger brief sequences of predefined actions)
Manual Operation (replication processes directly human-operated; humans exercise step-by-step control)

A6. Replication Control Complexity. This is intended to be a specific quantitative measure, e.g., a bit count or bit rate. This dimension represents a continuum of values with divisions applied as convenient. Thinking about complexity, von Neumann[3] wrote: "I am not thinking about how involved the object is, but how involved its purposive operations are. In this sense, an object is of the highest degree of complexity if it can do very difficult and involved things." See also dimensions B6 and B10.

Few bits required to control entire replication process

Many bits required to control entire replication process

A7. Replication Control Maintenance. As proposed by Szathmary,[2417] replicator goal maintenance may be achieved either by stochastic gravitation toward an "attractor" in the dynamic control space, or more directly by "storage" based control information (Section 5.1.4(5)). Warns Yudkowsky:[2452] "A critical question is what type of cybernetic control processes operate within the replicator. Even the simplest thermostat, from an information-theoretic perspective, is far less innocent than it seems. It can steer a large volume of starting microstates into a small volume of final microstates. It decreases entropy and hence adds information in the subsystem. It may turn out to apply a covert optimization effect. Error tolerance is the root of all evolvability. It deserves emphasis that not all optimization subprocesses or cybernetic control mechanisms may be recognized as such, unless subject to audit on the volume of the incoming and outgoing state space."

Replication control is loosely maintained by stochastic gravitation to an attractor in the dynamic control space (e.g., reaction networks)

Replication control is rigorously maintained by information storage-based systems (e.g., gene-like replicators)

A8. External Veto Authority. Replicators could be disabled or shut down by external signal or other means, maintaining creator control and contributing to public safety (Section 5.11). For example, the technical regulations[2453] for the highly-dangerous weapons-wielding "BattleBots" of televised competition fame[2454] include the following numerous provisions for safe operation and for regaining full human control of teleoperated or autonomous devices:

2.6.2 AUTONOMOUS BATTLEBOTS AND COMPONENTS — An autonomous function is one that moves the BattleBot or operates a weapon independently of any remote control input. Control feedback devices such as steering gyros and motor speed servos are not considered to be autonomous components. Autonomous BattleBots or autonomous components on a BattleBot are allowed, provided that: (a) When a BattleBot is activated, all autonomous functions are initially disabled, and require a specific remote command to become enabled. (b) The BattleBot's remote control system can be used to override and stop any and all BattleBot and weapon system autonomous motion. (c) All autonomous systems comply with the specifications of "3.1.2 Fail-Safe". (d) The BattleBot has a clearly visible external light to indicate when any autonomous function is enabled.

3.1.2 FAIL-SAFE OPERATION — All BattleBots require a robust fail-safe system that electronically or mechanically shuts off all motion-system and weapons power within one (1) second after the remote-control transmitter is switched off, or otherwise stops transmitting.

5.4.4 SECONDARY POWER SWITCH — All BattleBots are required to have a switch that allows the remote-control receiver power to be switched on and off independently of the primary-power Master Switch.

6.6.1 RADIO FAIL-SAFE — Upon loss of the remote-control signal, any ICE [Internal Combustion Engine] in a BattleBot has to either shut off (cease producing power) or begin returning to idle speed within one (1) second of signal loss.

6.6.2 AUTOMATIC MECHANICAL DISCONNECT — Any ICE in a BattleBot requires a centrifugal clutch or other mechanical disconnect mechanism designed so that, while the engine is running at idle speed, there cannot be hazardous movement of the BattleBot itself, or of any external weapon component driven by that engine. If a disconnect system is directly remote controlled, it has to automatically revert to a disconnected configuration if the remote control signal is lost.

6.6.3 REMOTE SHUT-OFF — Any ICE in a BattleBot must be able to be completely shut off (cease producing power) using the remote control.

Perhaps the most endearing illustration of the unfortunate results of a lack of external veto on artificial replicators may be seen in the animated Disney classic "The Sorcerer's Apprentice".* [2455]

Replicative capabilities and activities can be vetoed or terminated from outside the replicator device

Replicative capabilities and activities cannot be vetoed or terminated from outside the replicator device

A9. Embedded Replication Veto. Replicators could carry within them an automatic switch which prevents the conduct of replicative activities under certain well-defined circumstances. For example, environmental concerns[2458] that genetically modified plants might spread their genes to related crops in nearby fields led researchers to develop anti-crossbreeding systems such as the so-called "terminator technology" in genetically-modified crops,[2459] with only limited success.[2458,2460] In a more sophisticated approach,[2461] a "seed lethality" gene that prevents seeds of a tobacco plant from germinating is first inserted into the plant genome, resulting in a plant that still has normal growth and seed production. This plant is then crossed with another that has an added gene to repress the seed lethality gene, producing offspring plants with viable seeds that can continue to propagate indefinitely through self-pollination. But when these plants are crossed with normal tobacco plants the seed lethality gene and the suppressor gene are separated and the resulting seeds cannot grow, thus preventing further spread in the wild. Similarly, virotherapies using oncolytic viruses that are replication competent in tumors but not in normal cells offer a novel approach for treating neoplastic diseases.[2462]

Replicators contain an embedded functionality that prevents replicative activities under certain specified conditions.

Replicators contain no embedded replication veto functionality.

B. Replication Information

B1. Replication Information Autonomy. Most autonomous is the autocatalytic replication of spreading fire[264] and other

---

** The Sorcerer's Apprentice (which featured uncontrollably-growing numbers of animated brooms carrying water buckets) was loosely based on the writing of the German author and philosopher Johann Wolfgang von Goethe (1749-1832) in his 1779 ballad "Der Zauberlehrling" (The Magician's Assistant).[2456] The ballad was itself derived from the dialogue "Philopseudes" (The Lover of Lies)[2457] by the Greek satirist Lucian of Samosata (ca. 120-190 AD), and the original story probably dates back to ancient Egypt.*

reaction-diffusion systems[2463] that require no stored information to be present anywhere, although the information might be regarded as being embedded, or implicit, in the physical process.

- Replication information is stored offboard
- Replication information is stored partly offboard, partly onboard
- Replication information is stored onboard
- Replication information not explicitly stored anywhere

B2. Replicator Information Redundancy. How redundant is the information stored in the data cache? In biology, the radiation-resistant bacterium *Deinococcus radiodurans* includes a great deal of genetic redundancy[2464] to achieve high-fidelity DNA repair following severe radiation damage.

- Each cache contains all information in the entire data set
- Each cache contains overlapping subsets of the entire data set
- Each cache contains nonoverlapping unique data subsets of the entire data set
- Each cache contains data subsets of a subset of entire data set (i.e., some data not present in any cache)
- No cache contains data

B3. Replicator Information Centralization. How and where are the copies (if any) of the replication information stored in the replicator? Description-based reproduction with local memory will permit open-ended evolution with semantic closure, whereas template-based reproduction with distributed memory (i.e., copying via material self-inspection of its parts and identification of parts existing in the environment) allows only restricted evolution.[2378-2382]

- Data stored in 1 cache (maximally localized description-based reproduction)
- Data stored in multiple caches
- Data stored in many/all active subunits
- Data stored in many/all parts
- Data stored in no cache (template-based reproduction only)

B4. Replication Information Abstractivity.

- Information enabling replication is explicitly provided (e.g., a data cache providing instructions or descriptions)
- Information enabling replication only implicitly provided (e.g., replicator operates by inspecting itself or a physical duplicate, then derives replicative process steps by inference or "reverse engineering")
- No information enabling replication is provided

B5. Replication Information Type. Very simple procedural rules can sometimes produce seemingly complex results,[336] in effect encoding vastly more information than it would first appear. For example, a 100 kg human body mass would contain $\sim 10^{28}$ atoms and hence would require $\sim 10^{29}$ bits of raw structural information to describe, assuming random atom placement and random atom type. Yet a 100 kg human body (excluding data content of brain) can be adequately described by a chromosome set of developmental information containing just under $\sim 10^{10}$ bits of encoded information, and estimates of the data storage capacity of the human brain have ranged from 10^9 - 10^{18} bits (Section 5.10). The 11-19 orders-of-magnitude differential between the encoded structural information and the raw structural information is a measure of the degree of redundancy inherent in the human body structure, and suggests that the design is very robust against most minor structural changes.

- Explicit process information (step-by-step procedural instructions for building daughter device)
- Descriptive process information (abstract procedural instructions, requiring some interpretation)
- Structural information (detailed blueprint of daughter device)
- Developmental information (genetic information or "recipe" for producing a daughter device)
- Behavioral information (description of desired behavior of daughter device)
- No information

B6. Replicator Description Size. This is intended to be a specific quantitative measure, e.g., a bit count, as shown in Table 5.1 and elsewhere (Merkle;[210] *Nanomedicine*,[228] Table 2.1). (See also dimension A6.) For example, Paul and Joyce[1372] observe that the maximum possible information content of a nucleic acid species of length n (assuming a 4-base alphabet) is $\log_2(4^n)$, whereas that of a protein species (assuming a 20-residue alphabet) is $\log_2(20^n)$.

Many people believe that self-replicating systems must be extremely complicated, but the data show that this is not necessarily so. The data comprising almost any known replicator could easily be stored on a modern PC or laptop computer, and the descriptions of many replicators are less than 1 megabit in size. Note that although *Mycoplasma genitalium* has the smallest known genome of any free-living organism, not all of these genes are needed[2465] and the minimum possible genome may be only about one-third of this size.[1865] (*M. genitalium* is a 0.3-μm obligate parasite that lacks many functions needed for independent saprophytic life.) Many electromechanical devices that have been built over the years which demonstrate the ability to feed, metabolize, learn, respond to stimuli, recognize the self, and move about in physical space with goal-oriented behavior[178-181] are quite modest in complexity, possibly requiring as few as 30 bits[2466] to 90 bits[2467] for their physical description. (For example, machining the Penrose ratcheting 2-blocks[680] to 1% dimensional accuracy requires 7 bits per Cartesian vertex coordinate. With 2 coordinates (x, y) per vertex, and 11 and 15 distinct vertices on the two block types, respectively, the block pair can be described in 364 bits.) Joseph Jacobson at the MIT Media Lab suggests[1930] that the goal for the next decade of manufacturing technology development should be to "maximize complexity per unit volume — [we have] 6 orders of magnitude left to go in complexity of engineered systems."

Interestingly, in 1961 engineer Marcel Golay,[2468] evidently having von Neumann's kinematic replicator freshly in mind, wrote: "Suppose we wanted to build a machine capable of reaching into bins for all its parts, and capable of assembling from these parts a second machine just like itself. What is the minimum amount of structure or information that should be built into the first machine? The answer comes out to be of the order of 1500 bits — 1500 choices between alternatives which the machine should be able to decide. This answer is very suggestive, because 1500 bits happens also to be of the order of magnitude of the amount of structure contained in the simplest large protein molecule which, immersed in a bath of nutrients, can induce the assembly of those nutrients into another large protein molecule like itself, and then separate itself from it."

Table 5.1. Information required to describe some self-replicating systems (descriptions, file sizes, or genomes)

Self-Replicating System	Number of Bits Needed to Describe Replicator	References
Sommerfeld self-rep BASIC program	0.000016 x 10^6	424
Penrose ratcheting 2-blocks	0.000364 x 10^6	680 & see text
Subviral plant pathogen (viroid)	0.000492 x 10^6	1743
Burger et al. self-rep C program	0.000808 x 10^6	422
Murine cellular *PrP*^{C} (prion)	0.000998 x 10^6	1739
Rebek's self-replicating molecules	~0.001000 x 10^6	1617, 1619
Human *PrP* protein (prion)	0.001500 x 10^6	2469, 2470
Ray's evolved Tierra program	~0.010000 x 10^6	372
Poliovirus type 1, Mahoney strain (virus)	0.014866 x 10^6	1949, 2471
Human mitochondrion genome	0.033138 x 10^6	1825
Ebolavirus (virus)	0.037902 x 10^6	2472, 2473
Penrose ratcheting 12-blocks	~0.049000 x 10^6	681, 683
SARS coronovirus, Tor2 isolate (virus)	0.059502 x 10^6	2474
Mammalian 80S ribosome	0.073284 x 10^6	Section 4.2
Mushegian's minimal genome	~0.300000 x 10^6	1865
T4 bacteriophage (virus)	0.337806 x 10^6	2475
von Neumann's Universal Constructor	~0.500000 x 10^6	3, 210
1988 Internet worm	~0.500000 x 10^6	210, 2476
Nanoarchaeum equitans (archeon parasite)	~1.000000 x 10^6	2477
Mycoplasma genitalium (bacterium)	1.160148 x 10^6	1867
Pyrenomas salina (algae)	1.320000 x 10^6	1693, 2478
Hemophilus influenzae (bacterium)	3.660274 x 10^6	2479
Escherichia coli K-12 (bacterium)	9.278442 x 10^6	2480
Saccharomyces cerevisiae (yeast)	24.312602 x 10^6	2481
Merkle-Freitas Assembler (compressed)	**~50.000000 x 10^6**	**estimated**
Arabidopsis thaliana (mustard plant)	230.819898 x 10^6	2482, 2483
Drosophila melanogaster (fruit fly)	245.307954 x 10^6	2483, 2484
Merkle-Freitas Assembler (1 byte/atom)	**1,631.270984 x 10^6**	**Section 4.11.3**
Gallus domesticus (chicken)	2,400 x 10^6	1693
Petunia parodii (petunias)	2,442 x 10^6	2485
Mus musculus (mouse)	5,235 x 10^6	2486
Xenopus laevis (frog)	6,200 x 10^6	1693
Homo sapiens (human, male)	6,294 x 10^6	2487
Homo sapiens (human, female)	6,406 x 10^6	2487
Nicotiana tabacum (tobacco)	8,868 x 10^6	2488
Avena sativum (oats)	22,630 x 10^6	2485
Tulipa (garden tulips)	49,408 x 10^6	2485
Protopterus aethiopicus (marbled lungfish)	263,000 x 10^6	2493
NASA self-replicating lunar factory	272,000 x 10^6	2
Ophioglossum petiolatum (fern, a plant)	320,000 x 10^6	2489
Amoeba proteus (amoeba protozoan)	580,000 x 10^6	2490, 2492
Amoeba dubia (amoeba protozoan)	1,340,000 x 10^6	2490-2493
Chaos chaos (amoeba protozoan)	2,680,000 x 10^6	2492

B7. Replication Information Sharing. If replication information is present in the replicator, is it always present or only temporarily resident?

Replication information is never present within the replicator

Replication information is only transiently present within the replicator (e.g., "horizontal gene transfer"[2494-2496] with information markers sequentially shared among multiple units in a replicating consortium;[2497] see Section 5.3)

Replication information is always present within the replicator

B8. Replicator Information Lockout. Replication-related information, while present within the replicator, is encrypted or locked and thus not immediately accessible to the device. External signals may be sent to the device to unlock, de-encrypt, relock or re-encrypt all or part of the information, either in blocks or in total, or data accessibility may be enabled by other means — a crude analog of RNA interference in medicine.[2498]

Replication-related information is unlocked and unencrypted, and fully available for use by the replicator at all times

Replication-related information is locked or encrypted, but may be made accessible via remote signal or other means

Replication-related information is locked or encrypted, but may be made accessible only in limited blocks via remote signal or other means

Replication-related information is permanently locked or encrypted, or is never present

B9. Replicator Description Alphabet. In the case of biopolymer (e.g., DNA) synthesis, from both theory[2042] and experiment[2043] one expects higher fidelity of replication with smaller genetic alphabets than with large genetic alphabets. Multiple alphabets are also possible. For example, Rocha[2381] notes that if in addition to symbols standing for actions to be performed as in the DNA-based genetic code, the genetic system were to be allowed a second class of symbols standing for contextual or environmental measurements, “then a richer semiotics can be created which may have selective advantage in rapidly changing environments, or in complicated, context dependent, developmental processes.” Rocha[2499] observes that RNA editing[2500-2502] (wherein mRNA molecules contain information not coded in the DNA) may be seen as a mechanism for this type of contextual input that is already found in biology, at least for certain well known living organisms like the African trypanosomes[2503-2507] and as a potentially important mechanism in the morphogenesis of highly evolved animals.[2508]

Replicator carries no description (genome)
Replicator description (genome) is coded using a small alphabet of symbols
Replication description (genome) is coded using a large alphabet of symbols
Replicator description is coded using two or more distinct alphabets of symbols

B10. Replicator Triviality or Complexity. One simple definition of replicator triviality would be the ratio of replicator description bit count to the average parts description bit count, which compares parts complexity to the complexity of assembly operations. A low ratio implies that the embedding universe (including its physical laws of operation) or substrate contains most of the information required for replication to occur. A high ratio means that most of the information content of the replicator resides in its own organization, and not in its parts, or its surroundings, or in natural physical laws. (See also our discussion of the Fallacy of the Substrate, Section 5.5.) Sayama[2509] suggests this dimension may include two nearly orthogonal subdimensions: (1) the complexity of assembly tasks (e.g., complexity comparison between parts and final products) and (2) responsibility for assembly tasks (e.g., complexity comparison between how much the replicator does and how much the environment does, during replication).

Trivial = low ratio (replicator requires few assembly steps and is made of a small number of complex parts)
Nontrivial = high ratio (replicator requires many assembly steps and is made of a large number of simple parts)

A similar “typography of self-reproducers” has been proposed by Luksha,[2388] who distinguishes replicators based on the degree of complexity of self-reproducer S, quantified as c(S), as compared to the degree of complexity of the environment, quantified as c(E) (see Table 5.2).

Burks[4] addressed replicator triviality by proposing that “what is needed is a requirement that the self-reproducing automaton have some minimal complexity,” and suggested that a minimum bound on the complexity might be satisfied by the requirement that a “self-reproducing automaton also be a Turing machine.” Langton[359] rejects such a stringent requirement which he says not only “eliminates the trivial cases, but it also ... eliminates all naturally occurring self-reproducing systems as well” because none have been shown equivalent to a Turing machine. As noted by Adams and Lipson,[272] “though claims to the contrary exist,[2510] it does suggest that a view not reliant on a requirement for universal-computation could be worthwhile.”

Currently there are at least 30 different mathematical descriptions of “complexity“[496-504] and the concept is clearly of great importance in defining what is meant by “replication”.[2387] The Efstathiou group[2511] at the University of Oxford has developed theoretical models and simulations of the complexity of manufacturing systems. Future theoretical work should endeavor to distill all of these measures into a workable quantitative measure most applicable to kinematic replicators. Such a detailed distillation is a highly specialized topic worthy of investigation but unfortunately lies beyond the scope of this book.

B11. Replicator Pattern Instantiation Specificity. New et al[2512] note a distinction between structure-replicators and function-replicators. That is, can the replicator exist only as a specific physical instantiation, or is the replicator a pattern that is imposed on physical matter and can replicate independently of the precise composition of that solid matter while preserving all replicative functions (e.g., see also KCA-based replicators; Section 3.8)?

Replicator can exist only as a specific physical instantiation (e.g., “autocatalytic replicators” that produce exact copies of a template molecule, or assemblers that produce exact physical copies of themselves)
Replicator has parts that must be instantiated exactly (e.g., DNA) and other parts that can exist as any of a variety of similar structures (e.g., cell membrane)
Replicator exists as a pattern imposed on physical matter and can replicate independently of the precise composition of that solid matter, while preserving all replicative functions (e.g., “function replicators” that maintain a set of essential functions without replicating the identities of the functional moieties)

B12. Replication Information Context Tolerance. In biological replicators based on DNA, the same codon-based nucleotide sequence can often be read with a “frameshift” of one or two nucleotide bases and still code for viable, indeed essential, proteins. This concept may be generalized to include the viability of a replication-related descriptive sequence when it is read or executed in different ways. Replication information may also be made more compact by making the translation, interpretation or execution of replication instructions dependent upon the previous instruction(s) that have been processed, their order of processing, or the manner in which they were processed. An example of this in biology is rule context sensitivity in embryogeny.[2401] See also E9 and F7.

Table 5.2. Luksha’s typography of self-reproducers

c(E) vs. c(S)	Type of Self-Reproduction	Description	Examples
c(E) > c(S)	quasi self-reproducers	strictly dependent in reproduction on a system of higher complexity not produced as a part of its reproduction process	• viruses and genes • memes • computer viruses and computer “artificial life” (e.g., Tierra[442])
c(E) ~ c(S)	semi self-reproducers	autonomous complex systems requiring another comparably complex system to self-reproduce	• organisms with sexual divergence • (certain) organisms with parasitic reproduction
c(E) < c(S)	true self-reproducers	complex autonomous systems capable of self-reproduction in an environment of basic elements	• prokaryotic / eukaryotic cells • organisms with asexual reproduction • self-reproducing society[1850] • artificial self-reproducing plants[2]

Data related to replication may be transcribed or executed in several different ways, and still produce a viable offspring; context-sensitive or parameterized grammars

Data related to replication may be transcribed or executed in only one way to produce a viable offspring; context-free grammars

C. Replication Substrate

C1. Substrate Physicality. A virtual environment, which is purely computational, in fact also takes place in a material substrate, either a computer memory (based on silicon chips), or in our brain (based on neurons). However, replicators existing in such an environment are not kinematic replicators because their components do not engage in physical movements through space. This factor is interdependent with replicator physicality (see D1).

Physical Environment (physical matter)

Virtual Environment (purely computational)

C2. Substrate Naturalicity.

Wet (natural, biological, organic)

Hybrid Wet-Dry

Dry (artificial, nonbiological, mechanical)

C3. Substrate Technology Level or Granularity.

Subatomic ("femtotechnology"?)[2565-2567]

Atomic/Molecular: nanotechnology (nanoscale)

Microscale: MEMS (microns)

Macroscale: 20th century industrial (mm to meters)

Megascale: large space systems (km, megameters, etc.)

C4. Substrate Physical Dimensionality. This refers to the dimensionality of the portion of the substrate that is relevant to the productive part of the replicator's operations. Processes that take place on tool tips are pointlike (0-D), even though the tool as a whole might move through space in multiple dimensions with multiple degrees of freedom.

0-D (pointlike)

1-D (linear)

2-D (planar)

3-D (volumetric)

C5. Replication Substrate Phase. Replication takes place in some medium, or at the interface between two or more different media (see also "L6. Environmental Partitioning"). This dimension to some extent substitutes as a variable describing the relative randomicity of parts orientation in space or "jumbleness" of the parts presentation to the replicator ingestor subsystem (see Table 5.3) (see also "C10. Entropy of Substrate").

Table 5.3. Phase of matter in the material substrate

INTERFACE	Vacuum (V)	Photon (Ph)	Plasma (P)	Gas (G)	Liquid (L)	Solid (S)
Vacuum (V)	V-V	V-Ph	V-P	V-G	V-L	V-S
Photon (Ph)	Ph-V	Ph-Ph	Ph-P	Ph-G	Ph-L	Ph-S
Plasma (P)	P-V	P-Ph	P-P	P-G	P-L	P-S
Gas (G)	G-V	G-Ph	G-P	G-G	G-L	G-S
Liquid (L)	L-V	L-Ph	L-P	L-G	L-L	L-S
Solid (S)	S-V	S-Ph	S-P	S-G	S-L	S-S
No Interface	V	Ph	P	G	L	S

C6. Replication Substrate Temperature. At what temperature may replication take place on the given substrate? For example, if sufficient precision and reliability in diamond mechanosynthesis cannot easily be achieved at room temperature,[2325] then colder substrates (e.g., LN$_2$ temperature) may be required, further limiting the risks of runaway replication in the natural environment (Section 5.11).

Replication can only take place on a substrate maintained at temperatures near absolute zero, e.g., liquid helium

Replication can take place at or below cryogenic temperatures, e.g., liquid nitrogen (LN$_2$)

Replication can take place up to near room temperature, e.g., ~300 K

Replication can take place up to elevated temperatures, e.g., 500-700 K

Replication can take place up to the temperatures of hot gas or plasmas

C7. Substrate Sufficiency. One simple quantitative measure would be a dimensionless ratio for each parts type, defined as the relative concentration of a given part present in the substrate divided by the relative concentration of the given part in the replicator. This is a measure of how well the parts content of the substrate matches with the materials input requirements of the replicator, similar to the "extraction ratio" described by Freitas in 1980 (Freitas;[1014] Freitas and Gilbreath,[2] Section 5.3.6). For example, if a given part represents only 1% of the input substrate by volume, but that same part represents 10% of the volume of the replicator, then the substrate sufficiency for this part would be 1%/10% = 0.1, or 10%.

All replicator parts are present in the substrate in the exact proportions required for the construction of the replicator (most sufficient)

Replicator parts are present in the substrate in close but not exact proportions required for the construction of the replicator

Some replicator parts are present in the substrate in substantially different proportions from those required for the construction of the replicator (least sufficient)

C8. Environmental Fixture Requirement. The first teleoperated self-replicating machines constructed by Suthakorn[1284-1290] using LEGO® blocks required fixtures present in the environment to assist in parts-assembly processes. Similarly, Sayama[8,9] suggests including the construction of a replicator "workplace" as an integral part of the replication program in order to "enhance the robustness of self-replication processes...in our real, three-dimensional kinematic universe." (See also dimension I10 below.) In ecology, this procedure is known as "niche construction",[2513] as typified by the hive-building activities of bees or the dam-building activities of beavers. In reproductive physiology, the eggshell produced by bird or reptile parents serves "to stabilize the process of offspring construction by isolating it from the outside and holding it on a solid structure," and the uterus of mammals during reproduction similarly represents a workplace that "is included in the parent's body, but can be refurbished and extended as needed to hold its offspring while they are under construction."[8,9] Berkeley[182] also informally suggested the use of a robot "birth factory" for robot reproduction, in 1972.

- No fixtures, jigs, or workplace are required to be present in the environment for replication to occur
- Fixtures, jigs or workplace are required to be present in the environment for some replication processes to occur
- Fixtures, jigs or workplace are required to be present in the environment for all replication processes to occur

C9. Feedstock Import through Boundary. "Feedstock" constitutes all material inputs to the system, including materials whose atoms are destined for incorporation into finished products or temporary fixtures as well as other material inputs that might be used to supply energy, information, etc.

- Feedstock materials are not imported through any physical boundary
- Feedstock materials import through boundary permanently contaminates internal environment, preventing further replication processes
- Feedstock materials import through boundary temporarily contaminates internal environment; remediation of internal environment permits replication processes to continue
- Feedstock materials import through boundary is accomplished while continuously maintaining the integrity of the physical barrier, permitting replication processes to continue

C10. Entropy of Substrate. How disordered are the inputs that are presented to the replicator for assembly? See also B10.

- Substrate or input parts are located in fixed locations/orientations in space (e.g., parts anchored to fixed mounts)
- Substrate or input parts circulate through known locations/orientations in space according to a fixed schedule (e.g., parts presented on circulating conveyor)
- Substrate or input parts are constrained to specific regions of space but may be positioned randomly within that specific region (e.g., parts in bins)
- Substrate or input parts may be positioned randomly within the accessible physical space (e.g., parts in solution)

C11. Self-Replicability. Adams and Lipson[272,2514] have proposed a universal, continuously valued property of the interaction between a system and its environment, called self-replicability, representing the effect of the presence of such a system upon the future presence of similar systems. Their objective is to put self-replication on an algorithmically calculable, quantifiable, and continuous logarithmic scale that facilitates comparisons — both between the same system in different environments (determining ideal environments for a system's replication) and between different systems in the same environment (if optimizing self-replicability in a given environment is desired). Rather than viewing self-replicability as a property purely of the system in question, Adams and Lipson correctly view it as a property of the interaction between a system and its environment. They define replicability as a property relative to two different environments, which indicates the degree to which one environment yields a higher presence of the system over time. Self-replicability is then a comparison between an environment lacking the system and an environment in which the system is present.[272] A specific mathematical formula (too lengthy to detail here) is derived that can be universally applied to systems from cellular automata to living systems. Say the authors: "The flexibility of calculation reflects the idea that replication is a property of the information tied up in the interaction between a system and its environment, rather than in either one or in the specific physical makeup. Also, the crystal model in particular demonstrates how self-replicability succeeds in coinciding with intuition: The more likely it is for a system to manifest regardless of having been present before, the lower its self-replicability will be; conversely the more unusual and unlikely a system is which is capable of replicating its existence, the higher its self-replicability."

- Self-replicability < 0
- Self-replicability = 0
- Self-replicability > 0

C12. Fixture Acquisition. If fixtures are required, how are they obtained by the replicator?

- Fixtures are present everywhere in the environment
- Fixtures are available only in limited regions in the environment and the replicator must actively seek them
- No fixtures are present in the environment, so the replicator must produce its own fixtures by itself

D. Replicator Structure

D1. Replicator Physicality. This factor is interdependent with substrate physicality (see C1).

- Physical Device (kinematic replicator)
- Particle Device (kinematic-cell automaton)
- Virtual Device (cell automaton replicator or declarative program)

D2. Replicator Naturalicity. The relative advantages and limitations of "soft" vs. "hard" machines in growth and replication have been discussed by Drexler,[328] Freitas,[228] and Sosic and Johnson.[2515]

- Wet (natural, biological, organic)
- Hybrid Wet-Dry
- Dry (artificial, nonbiological, mechanical)

D3. Replicator Technology Level or Granularity. One interesting unconventional alternative is the quantum-dot-based "programmable matter" of McCarthy,[2516] which would involve physical substances made of artificial atoms whose elemental character is capable of being electronically switched.

- Subatomic ("femtotechnology"?)[2565-2567]
- Atomic/Molecular: Nanotechnology (nanoscale)
- Microscale: MEMS (microns)
- Macroscale: 20th century industrial (mm to meters)
- Megascale: Large space systems (km, megameters, etc.)

D4. Replicator Physical Dimensionality. Tool-tip AFM-based systems are 0-D; early Penrose blocks (Section 3.3, Figure 3.3) are 1-D; etc. This item refers to the physical dimensionality of the constructing, assembling, or manufacturing process, and not to the kinematic manipulator degrees of freedom described in H5. For "temporal dimensionality" of replicators, see L8 (heterochrony).

- 0-D (pointlike)
- 1-D (linear)
- 2-D (planar)
- 3-D (volumetric)

D5. Replicator Scale. Because of their superior speed of operation and thus their ability to build more finely-grained structures composed of vastly greater numbers of parts in a given volume per unit of time, microscale replicators constructed from nanoscale components should be capable of far greater replicative complexity than macroscale replicators constructed of macroscale parts. But replicators can be built at either scale.

- Subatomic (<0.1 nm)
- Nanoscale (0.1-300 nm)
- Microscale (0.3-1000 microns)
- Macroscale (1 mm -10 m)
- Megascale (>10 m)

D6. Replicator Mass. This quantity is a continuous measure.

- Subatomic ($<10^{-26}$ kg)
- Nanoscale (10^{-26}-10^{-16} kg)
- Microscale (10^{-16}-10^{-6} kg)
- Macroscale (10^{-6}-10^{6} kg)
- Megascale ($>10^{6}$ kg)

D7. Replicator Boundary. Compartmentation is regarded by many as essential for the origin of life[2517] and successful replication. Compartmentation can occur via a medium that limits macromolecular diffusion more than small molecule diffusion (e.g., the interior of a gel matrix, or a micro- or nano-porous rock),[2518] or via an emulsion in which small aqueous compartments in a non-aqueous matrix house replicating molecules,[2519] or via membranes or walls enclosing the replicator machinery.[2517] Interestingly, Barricelli[447] also predicted that his virtual symbioorganisms would need to develop means of controlling their local environment (such as an external membrane) if they were to evolve past a certain level of complexity.

- No isolation of replicator interior from external environment
- Replicator processes compartmentalized by a macromolecular diffusion-limiting medium
- Replicator processes compartmentalized by an emulsion containing medium and non-medium microregions
- Replicator processes compartmentalized by physical membranes or walls

D8. Product Export through Boundary. "In typical applications, the products of molecular manufacturing must be delivered to an external environment without permitting back contamination of the eutactic internal environment" of the assembler.[208] "Product" here may include both replicas and non-self objects manufactured by the original replicator.

- Product is not exported through any physical boundary
- Product export through boundary permanently contaminates internal environment, preventing further replication processes
- Product export through boundary temporarily contaminates internal environment; remediation of internal environment permits replication processes to continue
- Product export through boundary accomplished while continuously maintaining integrity of physical barrier, permitting replication processes to continue

D9. Replicator Structural Fixity. Internal components may be fixed or mobile within the replicator boundary, or they (most likely active subunits) may be free to exit the replicator boundary, possibly to return later. Replicators may fragment into non-growing entities that are considerably smaller than the whole viable entity, and these fragments may come together at a later time to form a viable organism. Alternatively, a replicator might fragment, with each disparate component incapable of growth but the population of components still capable of achieving success.[2520] Some plant RNA viruses exhibit just such a pattern,[2521] with each particle packaging separate RNA and sometimes three separate particles needed to establish an infection, though there are as yet no examples of this strategy among the prokaryotes. Size, shape, and morphology of a replicator composed of a facultative aggregate of active subunits may change according to the environmental and social status of the aggregate. One example of such an organism is *Myxococcus xanthus*,[2522] whose life cycle is carefully controlled by cell density and nutrient levels, and consists in turn of tiny forms, actively moving large forms, and huge social formations producing mushroom-like fruiting bodies.[2520] It is also proposed[2520] that nanobacteria may react to stress by becoming social and forming communities, or by "hibernating" for extensive periods waiting for suitable conditions permitting growth, or by forming and shedding units resembling viruses — an elementary system of tiny units performing special tasks. In this theory, only when united and surrounded by membrane, thus closing the compartment, would the putative nanobacteria resemble present forms of bacteria.[2520]

- Internal components occupy fixed relative structural positions within replicator boundary
- Internal components occupy constrained relative structural positions, but have some freedom of movement relative to each other within replicator boundary
- Internal components occupy no fixed relative structural positions, and are free to move relative to each other within replicator boundary
- Internal components not constrained to remain within replicator boundary

D10. Replicator Particity. Is the replicator composed of discrete parts, or is it constructed as a unitary block with no individual parts whatsoever?

- Replicator is built as a solid block of material without any discrete parts
- Replicator is composed of parts which are all of the same size
- Replicator is composed of a convergent sequence of progressively larger parts of uniform sizes within several distinct size classes
- Replicator is composed of a mixture of parts of various sizes

D11. Process Materials Storage. Where are process materials stored?

- Process materials are stored only inside the replicator
- Process materials are stored partly inside, partly outside, the replicator
- Process materials are stored only outside the replicator
- The replicator does not store any process materials

D12. Replicator Computer. Does the replicator possess an onboard computer (e.g., central processing unit (CPU) and general-purpose memory? Note that any CPU contains memory, and any memory requires a CPU (or at least logic).

Replicator possesses an onboard computer containing general-purpose memory and CPU

Replicator possesses simple fixed-purpose logic and memory of limited semantics

Replicator possesses no onboard computer

D13. Replicator Contiguity. Are the various components of a replicator contiguous in physical space, or not? Notes Friedman:[19] "There is an implicit assumption in much of the literature that the self-replicating machines must consist of a single complex assembly (that's almost what we see in nature if we ignore the complementary activity of the sexes.) In the engineering world, it appears abundantly more practical to envision a large, distributed set of cooperating elements, such as a modern industrial factory. Then it becomes interesting and practical to ask questions such as: 'What is the simplest factory that can manufacture a useful product and also manufacture a complete replication of itself (with and without human intervention)?' Or: 'What is the simplest factory which can self-replicate autotrophically (with and without human intervention)?' For the cases permitting human intervention at least we have an existence proof: The set of all factories in the United States can produce useful products and they — as a system — clearly have the ability to produce more of their own kind (or where else did they come from?). So far, there is no existence proof of the case without human intervention — except the biological analogy." See also I4.

Replicator consists of a single complex assembly that is spatially contiguous

Replicator consists of multiple assemblies that are spatially non-contiguous

E. Passive Parts

A passive part represents the most primitive component that is handled by the replicator, as it replicates or manufactures non-self product. It possesses no onboard power or control. Examples might include carbon dimers if the replicator uses dimers as a principal carbon source for mechanosynthesis,[2323] simple mechanical struts and gears if these are found in the replicator's environment, and so forth. The simplest passive parts are the most primitive components of which the replicator is constructed, and which the replicator is capable of manipulating for purposes of fabrication or assembly.

E1. Passive Constituent Parts Count. Refers to the total number of primitive passive parts which the replicator must individually manipulate in order to make a copy of itself. If the simplest parts used are atoms, as in molecular manufacturing, then the "parts count" becomes simply the number of atoms in the replicator structure, or "atom count."

1 part

2 parts

Many parts

Atom count

E2. Passive Constituents Parts Scale. This item refers to the scale of the most primitive passive parts from which the replicator can be said to be comprised, and which the replicator must individually manipulate in order to make a copy of itself.

Subatomic (<0.1 nm)

Atomic/Molecular (0.1-1 nm)

Nanoscale (1-300 nm)

Microscale (0.3-1000 microns)

Macroscale (>1 mm)

E3. Passive Constituent Parts Types. This item is intended to be a quantitative count of the number of distinct parts comprising the replicator. Of course, the number of distinct kinds of parts is not the sole measure of replicative complexity, just as reduced instruction set (RISC) processors are fundamentally simple but can still carry out very complex tasks. A nanodevice which replicated itself by manipulating atoms of all 92 natural elements could be said to have only 92 different "parts" (atoms), representing a fairly modest amount of parts diversity. The precise definition of "part" clearly depends on context. The Merkle-Freitas assembler (Section 4.11.3) may contain at most ~100 different parts types, and a modern jet aircraft contains more than 200,000 unique parts, each of them interacting with an average of 3-4 other parts.[2523] But in another view, for the case of the hydrocarbon nanofactory or molecular assembler (e.g., Section 4.11.3), as few as two "part types" might be said to be required (i.e., acetylene molecules plus one type of "vitamin" molecule).

All parts are of one type

Parts are of many types

Each part is of a unique type

E4. Number of Vitamin Parts. Vitamin parts are passive parts that cannot be manufactured by the replicator and must be provided from the outside in order for replication to be completed. In a "vitamin architecture," key materials (physical components or parts) essential for replication are exclusively provided from without (Section 4.3.7). Notes biochemist Michael Adams:[2524] "Obviously, no life-form survives in isolation from its surroundings, but organisms vary considerably in their dependence upon their environment. Thus, humans require at a minimum ten or so amino acids, various minerals, an array of biological cofactors (vitamins), and a continual supply of O_2 gas. Perhaps surprisingly, these same materials are also required by many microorganisms, although they typically differ from us in their ability to synthesize most, if not all, of the twenty amino acids as well as many, if not all, of what we term 'vitamins.' Like us, the vast majority of microorganisms require a fixed carbon source, which is usually a carbohydrate of some sort, although in some cases lipids, nucleotides, or various simple organic compounds are utilized. In contrast, some microorganisms are intensely dependent upon their environments. For example, some microbial parasites do not synthesize any amino acid or lipid, and only a few enzyme cofactors and nucleotides; rather, they obtain all of these compounds from their host." The need for essential vitamin parts can serve as a valuable replication safety mechanism. For instance, one species of therapeutic gut-dwelling genetically engineered bacteria[2525] has had its gene for thymidine synthesis removed. The modified bacteria can survive only in the gut where thymidine is naturally available; outside the gut where thymidine is not available, the altered bacteria die in just 72 hours.

One common safeguard used to provide total control over artificial cells is to make their lives dependent on chemicals that do not exist in the environment — withdrawing the critical chemicals would result in the death of the cells, particularly if they should escape into the environment.[3107]

- No vitamin parts are required for replication
- A few vitamin parts are required for replication
- Many vitamin parts are required for replication
- All parts required for replication are vitamin parts

E5. Replicator Nutritional Complexity. How many different sorts of parts can the replicator eat, and still successfully proliferate? This includes two closely related issues:[414] (a) minimal nutritional complexity, and (b) nutritional diversity or flexibility. The small-genome 0.17 μm^3 marine bacterium *Brevundimonas diminuta* can only grow on a few kinds of sugars and amino acids;[2526] *C. oligotrophus* eats primarily hydrocarbons that number many in type, though the precise complexities of its metabolism are currently unknown;[2527] while the ~1 μm^3 *E. coli* can consume very many substrates and has 285[2528] or more (considering unknown sequences) different transport systems to accumulate them. M. Krummenacker[414] notes that the champions of minimal nutritional complexity in the biological world are probably the photoautotrophic cyanobacteria,[2529] whose energy source is light and whose sole carbon source is CO_2 — though these (and other microbes mentioned earlier) also require a number of trace minerals including metal ions, phosphorus, nitrogen and sulfur in addition to the carbon source. Genome size appears related to nutritional complexity.[2527]

- Replicator can replicate only if fed one specific menu of material inputs
- Replicator can replicate if fed any one of several menus of material inputs
- Replicator can replicate if fed a diverse menu of material inputs

E6. Required Parts Preparation. According to Chang:[793] "Like other robotics researchers, Dr. Rodney Brooks, director of the Artificial Intelligence Laboratory at the Massachusetts Institute of Technology, predicts the development of robots that assemble themselves, so to speak, out of ready-made parts." Using pre-made parts is not "cheating": Virtually all known replicators — including human beings — rely heavily on input streams consisting of "premanufactured parts" most of which cannot be synthesized internally. Indeed, the development of artificial replicators that do not require premanufactured parts seems unnecessary, more technologically challenging, and quite possibly a threat to public safety.[2909] Notes Merkle:[793] "Should we relinquish autonomous, self-replicating devices that can function in a natural environment? The answer is yes, that looks like a fine thing to relinquish." And replication from more disordered starting materials is harder work and thus likely harder to engineer. If the length of its genome was an approximate measure of the difficulty of an organism's function, then we might infer that the autotrophic flowering plants, many of which have surprisingly large genomes compared to animals of comparable size (Table 5.1), must have much greater difficulty manufacturing organic nutrients from less organized matter than do animals who must catch prey for food.[20] However, the situation is not so clear because certain DNA sequences are repeated hundreds or thousands of times, and apparently only a small fraction of the nuclear genome of plants with large genomes is transcribed — e.g., Robert B. Goldberg of UCLA estimates that only 1-2% of the tobacco nuclear genome is transcribed, based on hybridization of RNA to genomic DNA.[2530]

- Replicator parts cannot be fabricated onboard, but must be supplied from the outside as completely prefabricated parts
- Replicator parts cannot be fabricated onboard, but externally-supplied prefabricated near-parts can be reworked onboard into the necessary finished parts
- Replicator parts may be fabricated onboard from relatively crude feedstocks
- Replicator parts may be fabricated de novo from significantly disordered natural environmental materials (e.g., rocks, air, biological substances)

E7. Passive Parts Complexity. A crude single quantitative measure would be the average descriptive complexity per part — e.g., the bits required to describe each part at the blueprint level of detail, summed over all part types, divided by the number of parts types. Alternatively, this measure could be reported as a histogram, e.g., showing the number of parts as a function of bits per part. A relative measure, such as the ratio of the average parts complexity to the total replicator complexity, might also be useful. Notes Aristides Requicha[2531] of the USC Laboratory for Molecular Robotics: "When you replicate something, the complexity of the components you are allowed to use is very important. Suppose, for example, that you replicate DNA by using a long strand as template to 'catalyze' the ligation of two others that are pretty complex. You may call this replication, but the problem is going to be in getting the two component strands. Where do these components come from? In other words, the final act of replication may not be the most interesting part of what is going on, it may be kind of trivial compared with making the components."

- Parts are very simple and of low informational complexity
- Parts are of moderate complexity
- Parts are very structurally complex and require large amounts of information to completely specify

E8. Parts Precision. This item refers to the precision with which parts must be fabricated (e.g., minimum feature size), as distinguished from the overall size of the parts themselves (E2). See related dimension E11.

- Parts are fabricated to molecular precision
- Parts are fabricated to nanometer-scale precision
- Parts are fabricated to micron-scale precision
- Parts are fabricated to millimeter-scale or only macroscale precision

E9. Multiple Utility of Passive Parts. See also B12 and F7.

- Parts each have only one functional use.
- Parts each have two unrelated functional uses.
- Parts each have many unrelated functional uses.

E10. Parts Presentation. Do parts come to the replicator for assembly, or does the replicator go out and gather parts? Does the replicator have independent mobility? See also F8.

- Parts circulate freely in the workspace, akin to diffusive transport; replicator resides in one fixed location and samples the stream of parts as they go by
- Both parts and replicators circulate throughout some or all of the workspace, with some constraints or with no constraints on physical location
- Parts are assigned to fixed locations in the workspace, akin to a parts bin or warehouse; replicator circulates freely to gather needed parts

E11. Mode of Dimensional Specification. Digital specification of replicator parts is possible using such materials as LEGO®

blocks, molecular building blocks, or especially individual atoms during molecular manufacturing. Analog specification relates to bulk machining and similar non-modular manufacturing processes. See related dimension E8.

- Parts are specified by approximate dimensions (analog specification)
- Parts are specified by precise count of modular materials (digital specification)

F. Active Subunits

An active subunit is a replicator component that possesses power, control, or autonomous mechanical action. Examples might include a complete manipulator arm or an onboard computer, if the replicator design includes such components, up to and including whole autonomous robots if these are components within the entire replicator system. In biology, a single cell could be regarded as an active subunit of a multicellular organism.

F1. Multicellularity. Quantitatively, the item here represents the number of active subunits comprising a replicator, and may range from one single subunit up to thousands, billions, or more active subunits. In biology, modularity may improve the adaptability of complex adaptive systems.[2532] This is similar to Szathmary's[2417] dimension of "set" which distinguishes replicators according to the set of entities capable of replication (i.e., solitary vs. ensemble replication) and Segre's[2398,2427] ensemble replicators (Section 5.1.4). Szathmary and Wolpert[2533] have reviewed the evolution of multicellularity in biology.

- Unicellular (replicator consists of a single active unit)
- Multicellular (replicator consists of multiple active cooperating units)

F2. Active Subunits Scale. How large are the active subunits?

- Subatomic (<0.1 nm)
- Atomic/Molecular (0.1-1 nm)
- Nanoscale (1-300 nm)
- Microscale (0.3-1000 microns)
- Macroscale (>1 mm)

F3. Active Subunits Types. How many different types of active subunits are there? Subunits may also be organized in a functional hierarchy, as suggested by Miller[2393] (Section 5.1.2).

- Replicator has no active subunits
- All active subunits are of one type
- Active subunits are of multiple types
- Each active subunit is of a unique type

F4. Active Subunits Complexity. A crude quantitative measure would be the average descriptive complexity per subunit — e.g., the bits required to describe the assembly of each subunit from its constituent passive parts at the blueprint level of detail, summed over all subunit types, divided by the number of subunit types. A simpler but less useful measure would be the number of individual parts present in active subunits, possibly computed on a per-subunit basis. (See also E7.)

- Subunits are very simple and of low informational complexity
- Subunits are of moderate complexity
- Subunits are very structurally complex and require large amounts of information to completely specify

F5. Subunit Fate. Early in the replication process, groups of active subunits (e.g., cells) might be undifferentiated and thus may be called "precursor" subunits. Their fates can be assigned in several ways, frequently through receiving messages from an outside subunit called an "organizer". If precursor subunits each take on one of two fates, A or B, then a variety of static and signal-based strategies are possible.[2401,2534]

Graded Induction: A signal is released from an organizer in a graded pattern. The precursor subunit receiving the most signals assumes fate A, while those receiving fewer signals assume fate B.

Two Step Induction: The organizer first releases a uniform signal to all precursor subunits to let them know that they form a precursor group. A secondary signal is subsequently released to a subset of the group to further distinguish fates.

Sequential: The signal from the organizer reaches only a single precursor subunit, which assumes fate A. It then sends secondary signals to adjacent precursor subunits, giving them secondary identities.

Self-organization: The precursor subunits signal each other and the dynamic properties of the network of signals assigns fates, without any organizer subunit necessary.

Prepattern: Gene expression alone, deriving from each precursor subunit's lineage, is responsible for fates. Signals are not utilized, that is, the state of the parent subunit fully specifies the states of its progeny.

Chris Langdon[2535] observes that in multicellular organisms, the individual subunits (cells) not only self-replicate but also differentiate into specialized subunits that arrange themselves into a specific macroscale pattern of organization. It would seem that a complex assembler or nanofactory might similarly use post-replication differentiation of subunits to produce other complex nanofactories like itself. "Borrowing this neat trick from nature would require a distinction between germ-line 'cells' and body-line 'cells'," notes Langdon,[2535] "but such a scheme would seem to be well within the complexity envelope established by many of the other proposals presented in this book, especially in Chapter 4."

F6. Subunit Targeting. Not only must active subunits reach their proper physical locations during replication, but they must also accurately connect to other subunits.[2401] An example in biology is the nervous system, where developing proper connectivity is crucial.[2536] In order to create a working network of cells, cell extensions such as axons and dendrites must ultimately reach their intended targets. Targeting of cell extensions is usually based on one of two primary strategies.[2537,2538]

Specific Identity: The absolute location of a target is specified directly in the genetic code or replication instructions, e.g., a target may be located based on a chemical marker.[2401]

Relative Position: The relative location of a target is specified in the genome, so that the extension grows a specific distance and angle in order to reach the target. In biology, highly regular patterns of connectivity such as neural self-organizing maps (SOMs), are likely to form this way.[2401]

F7. Multiple Utility of Active Subunits. See also B12 and E9.

- Subunits each have only one functional use.
- Subunits each have two unrelated functional uses.
- Subunits each have many unrelated functional uses.

F8. Subunits Presentation. Do active subunits come to the replicator for assembly, or does the replicator go out and gather active subunits? See also E10.

Subunits circulate freely in the workspace, akin to diffusive transport; replicator resides in one fixed location and samples the stream of subunits as they go by
Both subunits and replicators circulate throughout some or all of the workspace, with some constraints or with no constraints on physical location
Subunits are assigned to fixed locations in the workspace, akin to a parts bin or warehouse; replicator circulates freely to gather needed subunits

F9. Process Functionality of Active Subunits. Do active subunits composing the replicator process matter, information, or both?

Active subunits are primarily kinematic in function (e.g., pure teleoperation of physical replicator through mechanical links)
Some active subunits have kinematic function, while others process information
All active subunits process information only (e.g., cellular automata)

F10. Timing of Subunit Activation. When are subunits activated during the replicative process? See also I8.

Active subunits are always activated
All active subunits are activated during self-replication
Some active subunits are activated during self-replication
Active subunits are activated after self-replication is complete

G. Replicator Energetics

G1. Process Energy Autonomy.

Unpowered (thermal vibrations only)
Remote Powered (offboard energy source)
Autonomously Powered (onboard energy source)

G2. Process Energy Redundancy. This refers to the number of onboard energy conversion mechanisms — as for example the number of independent glucose engines inside each respirocyte.[229] Replicator reliability is enhanced by providing greater redundancy of onboard energy sources.

Any source of energy can, by itself, power the whole replicator
Multiple sources of energy, each by itself, can power the whole replicator
No source of energy, acting by itself, can power the whole replicator (some/all sources must contribute to achieve powered operation of the whole replicator)

G3. Process Energy Centralization. How many sources of energy are there?

No source of process energy (thermal vibrations only)
Single source of process energy
Multiple sources of process energy
Many/all subunits can provide process energy
Many/all parts can provide process energy

G4. Number of Onboard Process Energy Types. How many different types of energy are employed? A replicator which is capable of replicating using multiple kinds of energy (e.g., chemical, acoustic, photonic, etc.) is more versatile and can operate in a greater range of environments and conditions, and is probably also more complex, hence is less likely to remain "inherently safe" (Section 5.11).

No source of process energy (thermal vibrations only)
All onboard process energy is of one type
Onboard process energy is of multiple types

G5. Process Energy Types. A matrix of power conversion processes that might be employed by replicators is readily defined (*Nanomedicine*,[228] Section 6.3 and Table 6.2).

Thermal
Mechanical
Acoustic
Chemical
Electrical/Magnetic
Photonic
Nuclear

G6. Process Energy Storage. Can energy be stored onboard the replicator (e.g., in batteries)? If energy can be stored onboard, can those stores be replenished during normal operations?

No onboard energy storage (power is used as received)
Energy can be stored onboard but cannot be replenished during normal operations
Energy can be stored onboard and can be replenished during normal operations

G7. Process Energy Efficiency. This factor is intended to be a quantitative measure of the amount of energy consumed in a single replication, possibly scaled to system mass, called the "energy efficiency" or more particularly the "specific energy for replication" (ε). For example, the synthesis of one ($M_{microbe} = 2.5 \times 10^{-16}$ kg) *E. coli* cell from glucose may consume three times the microbe's weight in glucose (4.2×10^{-9} μmoles),[2539] or $E_{microbe} = 1.2 \times 10^{-8}$ J, giving an energy efficiency of $\varepsilon_{microbe} = E_{microbe} / M_{microbe} =$ **4.8×10^7 J/kg** for replication. This is very good for an irreversible process, when compared to the range of $\varepsilon \sim$ **10^5 J/kg** (for practical nearly-reversible mill-style manufacturing processes; *Nanosystems*,[208] Section 13.3.7.b) to $\varepsilon \sim$ **10^8 J/kg** for chemical transformations envisioned for molecular manufacturing (*Nanosystems*,[208] Section 13.3.7.b; *Nanomedicine*,[228] Section 6.5.6(B)). By contrast, the first-generation Merkle-Freitas molecular assembler (Section 4.11.3.1) would be very energy inefficient, consuming $E_{M\text{-}F} = 1.49\text{-}5.93 \times 10^{-5}$ J to replicate one $M_{M\text{-}F} = 3.90826 \times 10^{-15}$ kg device, a much poorer energy efficiency of $\varepsilon_{M\text{-}F} \sim$ **$0.38\text{-}1.5 \times 10^{10}$ J/kg** for a single replication. Note that in biological systems of mass M, replicator metabolic rate B (watts) $\sim k_{met} M^{3/4}$,[2540] hence the specific energy for replication scales as $\varepsilon_{rep} \sim k_{met} \cdot \tau_{rep} \cdot M^{-1/4}$ (J/kg), where τ_{rep} is replication time and k_{met} is a proportionality constant. Since $\tau_{rep} \sim M^{1/4}$ (Figure 5.6), then ε_{rep} is independent of mass, at least for biological replicators. The possibility that different scaling laws might apply to molecular assemblers or nanofactories should be investigated further (Sections 5.2 and 5.9.5).

Process energy efficiency can also be scaled to system information content. For example, following a related suggestion by C. Phoenix[572] we can define an alternative dimensionless measure of energy efficiency (perhaps to be called the "replication informatic energy ratio" or ε_I) as the ratio of the amount of energy actually used to manufacture a replica to the kT entropic value of the information needed to describe the replicator. The most efficient possible replicator would have a ratio of $\varepsilon_I = 1$. Taking T = 300 K as the operating temperature, an *E. coli* requiring $I_{microbe}$ = 9.278442 x 10^6 bits to describe (ignoring genomic redundancy; Table 5.1) has a replication informatic energy ratio of $\varepsilon_I = E_{microbe} / (kT \ln(2) \cdot I_{microbe})$ = **4.5 x 10^5**. The Merkle-Freitas molecular assembler requires $I_{M\text{-}F}$ ~ 50.0 x 10^6 bits to describe (assuming data compression; Table 5.1), yielding a replication informatic energy ratio of only $\varepsilon_I = E_{M\text{-}F} / (kT \ln(2) \cdot I_{M\text{-}F})$ = **1.0-4.1 x 10^8**, or 2-3 orders of magnitude less energy efficient than *E. coli*. Note that "replicators that are inefficient in structure (e.g., [molecular assemblers or nanofactories] using vast blocks of diamondoid) will also be inefficient by this measure, since such non-complex structure will not require many bits to specify."[572]

- Minimal amount of energy consumed to achieve one replication (very efficient)
- Moderate amount of energy consumed to achieve one replication
- Large amount of energy consumed to achieve one replication (very inefficient)

G8. Replicative Energy Commitment. What percentage of total processing energy is devoted to replicative activities? In biology, larger replicators generally use a lesser fraction of their total systemic energy for reproduction than do smaller replicators.[2541]

- Replicative processes consume substantially all of replicator process energy
- Replicative processes consume a moderate proportion of replicator process energy
- Replicative processes consume only a tiny proportion of replicator process energy

H. Replicator Kinematics

H1. Process Manipulation Autonomy.

- Parts/subunits moved by random thermal forces only
- Parts/subunits moved by external forces applied to the part/subunit and directly controlled from outside the replicator
- Part/subunit motions selected and powered by internal mechanisms other than the part/subunit itself
- Parts/subunits moved by internal force applied by the part/subunit itself (i.e., parts/subunits move themselves)

H2. Process Manipulation Redundancy. As with G2, replicator reliability is enhanced with greater redundancy of onboard manipulator systems.

- Any onboard manipulator can, by itself, provide all process manipulation operations required to achieve replication
- Only a few onboard manipulators, each by itself, can provide all process manipulation operations required to achieve replication
- No single onboard manipulator can provide all process manipulation operations required to achieve replication (some/all manipulators must contribute to achieve replication)

H3. Process Manipulation Centralization.

- No source of process manipulation (random thermal forces only)
- Single source of process manipulation
- Multiple sources of process manipulation
- Many/all subunits can provide process manipulation
- Many/all parts can provide process manipulation

H4. Number of Manipulator Types.

- No onboard manipulators
- All onboard manipulators are of one type
- Onboard manipulators are of multiple types
- Each onboard manipulator is of a unique type

H5. Replicator Manipulation Degrees of Freedom.

- No onboard manipulators
- 1 DOF
- 2 DOF
- 3 DOF
- 4 DOF
- 5 DOF
- 6 DOF
- >6 DOF
- Hyperredundant manipulators

H6. Assembly Mechanism Style. At an operating frequency of ~1 MHz, assembly of molecular-moiety building blocks onto a workpiece across 10-nm pathlengths dissipates ~0.001 pW using mill-type mechanisms and ~0.1 pW using manipulator-type mechanisms, though for 100-atom building blocks both device classes may dissipate ~0.001 pW per atom moved (*Nanosystems*,[208] Sections 13.3.7.a and 13.4.1.f). Similarly, mill-type mechanisms appear to be at least an order of magnitude more productive per unit mass than manipulator-type mechanisms[208] — e.g., at ~1 MHz at 10-nm pathlengths, a typical 250,000-atom mill assembler could emplace ~10^6 feedstock atoms/sec on a workpiece giving a productivity per unit mass (kg/sec per kg/assembler) of ~4 assemblers/sec, whereas a typical 5,000,000-atom manipulator assembler could emplace 5 x 10^5 feedstock atoms/sec on a workpiece giving a productivity per unit mass of only ~0.1 assemblers/sec, a ratio of ~40:1 in relative productivity per unit mass. However, manipulator systems are far more versatile than mill systems (Section 5.9.6). This dimension may be generalized to describe, more broadly, programmable vs. hard-coded assembly actions.

- Mill-style assembly (high-frequency assembly of nanoscale components using repetitive operations on standard building blocks) (aka. hard-coded assembly, e.g., enzymes)
- Mixed-style assembly (using both hard-coded and programmable assembly systems, e.g., living cells)
- Manipulator-style assembly (lower-frequency assembly of nanoscale, mesoscale and larger components using programmable operations on standard or nonstandard building blocks) (aka. programmable assembly, e.g., ribosomes)

H7. Positional Accuracy. The need for manipulator positional accuracy varies as a function of the building blocks being manipulated. High accuracy is required to manipulate small parts that require precise alignment, whereas only low accuracy may be required for large parts designed to tolerate greater imprecision during assembly. This dimension could be quantified either as a relative measure of positional accuracy as against parts dimensions, or else as an absolute measure of positional accuracy in nanometers, microns, millimeters, etc. For example, diamond mechanosynthesis on the C(110) diamond surface probably requires C_2 dimer positional placement accuracies on the order of 0.2-0.5 Å.[2324,2325] See also E2, E8, E11, and F2.

Manipulators used for positional assembly have high positional accuracy

Manipulators used for positional assembly have intermediate positional accuracy

Manipulators used for positional assembly have low positional accuracy

I. Replication Process

I1. Replicative Influence. Can the replicator influence the probability that its own successful replication will occur? (Section 5.1.1)

Replicator exerts no influence on the probability of its own replication

Replicator exerts some influence on the probability of its own replication

Replicator exerts maximum influence on the probability of its own replication

I2. Replicator Activity/Passivity. Does the replication process occur probabilistically (stochastically) or deterministically? For example, enzymes depend on random diffusion events, whereas molecular mills and nanomanipulator arms operating in a vacuum environment demand positionally-precise actively-controlled tool tips.

Autocatalytic Assembly (replication occurs passively due to random forces; only end state is specified)

Directed Self-Assembly (replication driven by random forces, but guided or limited by jigs or other purposely imposed constraints)

Positional Assembly (replication driven actively by purposeful positionally-controlled actions; pathway to end state fully specified)

I3. Replicator Parasiticity. Viral or parasitic character of the device, defined along a continuum; alternatively, the number of "vitamin processes" (processes not accessible to the replicator internally), ranging from no vitamin processes to all vitamin processes. Extreme specialization for replication in a single particular external environment allows a replicator to eliminate many otherwise essential subsystems, thus making that replicator highly dependent on the chosen substrate and vulnerable to failure if the substrate is later altered in any way. Taking natural human endoparasites as an interesting biological analogy, Knutson[2542] notes that "when a parasitic creature takes up a serious parasitic lifestyle, it is likely to lose some important things. It loses its external skin (epidermis) because it has to be able to absorb food through its body surface. It loses most of its nervous system, just as creatures that live in the darkness of caves for thousands of generations are likely to lose their eyes. It loses its digestive system because all food is conveniently predigested by the host. And it may lose its capacity to move in favor of a capacity to just hang on....Adult tapeworms exemplify the extreme losses suffered by parasites. Their bodies are almost totally dedicated to the development and use of their reproductive apparatus. They lack digestive systems, since they mostly absorb already digested food; they lack the sort of skin we assume is on the outside of all creatures, since they must soak up food through their surface. They don't have a serious nervous system or muscles. Rather than being a single organism, a tapeworm is more like a giant colony of parts, each capable of independent activity."

Interestingly, the U.S. Patent Office Manual, in sections pertaining to the rules for deposits of "biological materials" for patent purposes,[2543] distinguishes nonparasitic and parasitic replicators: "Biological material includes material that is capable of self-replication either directly or indirectly. Direct self-replication includes those situations where the biological material reproduces by itself. Representative examples include bacteria, fungi including yeast, algae, protozoa, eukaryotic cells, cell lines, hybridomas, plant tissue cells, lichens and seeds. Indirect self-replication is meant to include those situations where the biological material is only capable of replication when another self-replicating biological material is present. Self-replication after insertion in a host is one example of indirect self-replication. Examples of indirect replicating biological materials include viruses, phages, plasmids, symbionts, and replication defective cells."

"Replication processes" may include assembly or fabrication processes, where fabrication is the construction of parts and assembly is the rearrangement of parts. All kinematic replicators must engage in either fabrication or assembly activities, or possibly both. But not all replicators must engage in fabrication (e.g., when parts are externally provided, thus requiring only assembly activities) and not all replicators must engage in assembly (e.g., when the replicator has a unitary design (see D10) with no individual parts, thus requiring only fabrication activities).

All replication processes performed by replicator only — includes onboard all manufacturing machinery required for replication (fully self-sufficient)

Replication processes are performed jointly by replicator and external entities — includes onboard some but not all manufacturing machinery required for replication

All replication processes performed by external entities only — includes onboard none of the manufacturing machinery required for replication (fully parasitic)

I4. Replication Process Centralization. Are replication processes concentrated in a single entity or subsystem, or instead distributed to multiple entities or subsystems? In highly decentralized replication, swarm construction[2544] may be used to build "complex, composable structures" as is demonstrated by termites and other social insects. See also D13.

One robot or subunit (among many) performs all replication activities (e.g., a single "assembler" device)

Multiple robots or subunits (among many) perform some/all replication activities (e.g., a two-subunit replicator composed of a "fabricator" subunit that synthesizes parts from molecular feedstock, cooperating with an "assembler" subunit that assembles parts into working fabricator and assembler subunits; Section 4.18)

All robots or subunits perform some/all replication activities (e.g., a "swarm" or factory device)

I5. Replication Process Specialization. Mill-style assembly processes involve highly specialized and purely repetitive operations which produce standard building blocks, whereas manipulator-style assembly processes involve more generalized "programmable operations that can stack these building blocks to make a wide variety of products."[208]

Replication processes performed by general-purpose entities, each of which is capable of performing all necessary processes

Replication processes performed by narrow-purpose entities, each of which is capable of performing only some necessary processes

Replication processes performed by highly specialized single-purpose entities, each of which is capable of performing only one necessary process

I6. Replication Process Timing. When does the replicator replicate, and when does it do nonreplicative activities, during its life-cycle?

Replicator undertakes replicative activities first, then undertakes nonreplicative activities (e.g., useful production)

Replicator undertakes replicative and nonreplicative activities at the same time, or in recurrent sequence

Replicator undertakes nonreplicative activities (e.g., useful production) first, then undertakes replicative activities

I7. Replication Goal Specialization. Despite the well-known human preoccupation with sexual matters, human physiology devotes surprisingly little mass directly to the organs of reproduction. Specifically, the 70,000 gm reference male body has only 40 gm of testes and ~60 gm of flaccid penis, totaling only ~0.14% of body mass. The nongravid 58,000 gm reference female body has 35 gm of uterus, 8 gm of ovaries, and perhaps ~50 gm of vagina, again only ~0.16% of total body mass (*Nanomedicine*,[228] Table 8.9). In other words, >99.8% of human body mass does not directly execute organismic replicative processes. Human tissue cells are slightly more specialized to the goal of cell reproduction, with ~3.4% of tissue cell mass devoted to the nucleus (*Nanomedicine*,[228] Table 8.17). Functional proteomics[2545] indicates that *Caenorhabditis elegans* uses 6% of its open reading frames to encode proteins required for cell division.

Of course, Dawkins would argue that all of an organism's mass executes replicative processes in one way or another, and that the above direct/indirect dichotomy is artificial. For example, during pregnancy a woman's body may raid itself for necessary minerals,[2546] hence the medically unsubstantiated[2547] old adage and myth that a woman loses "a tooth for every child".[2548] (In reality, calcium to build fetal teeth, when in short supply from the maternal diet, is absorbed from the mother's bones, not from her teeth.[2549] Although orthodontic tooth movements are slightly greater during pregnancy,[2550] apparently there is no direct mechanism for the physiologic withdrawal of calcium from teeth as there is from bone, so a developing fetus cannot calcify at the expense of the mother's teeth).[2551] But metabolic processes that withdraw nutrients are not unique to pregnancy and hence cannot logically be ascribed to replicative processes per se — the human body frequently raids its stores of specific nutrients (e.g., glucose, fat, iron, etc.) during times of physiological stress or unusually high demand.

Replicator structure and function designed exclusively to execute replicative processes

Replicator structure and function designed to execute both replicative and nonreplicative processes

Replicator structure and function designed almost exclusively to execute non-replicative processes

I8. Replication Process Subunit Assistance. At what point during its construction can a daughter replicator begin assisting in the construction of other replicators? See also F10.

Only complete replicators can perform replication activities (discrete replication)

Incomplete replicators can assist in replication activities

Subunits of replicators can assist in replication activities

Replicator parts can assist in replication activities (e.g., by serving as jigs)

I9. Replicator Parentage. How many replicators cooperate in the building of a daughter device? For example, Parham[2552] suggests 6-8 parent devices might be useful, though most proposals and most natural systems typically invoke only one or two active parental replicators.

Each daughter is built by only one parent replicator in the local replicator population

Each daughter is built by many parent replicators within the local replicator population

Each daughter is built by all replicators in the local replicator population

I10. Replication Process Intermediaries. An example in biology is the life cycle of slime molds, in which many originally independent cells must come together to form the slug and then the fruiting body, which then make many spores which become independent cells.[2412] Using replicators to build a robot factory which then builds the original replicator was an early strategy first quantitatively explored by Freitas[1014] in 1980. Sayama[9] proposes enhancing the robustness of self-replication processes "by introducing an additional subsystem that constructs a workplace prior to automaton construction." (See also C8 above.)

Replicator directly produces the daughter replicator device

Replicator builds one intermediate device which then builds or helps build the daughter replicator device

Replicator builds many intermediate devices which then build or help build the daughter replicator device

Replicator builds a robot factory which then builds or helps build the daughter replicator device

I11. Replication Auxeticity. During the nineteenth century, the discovery that cells reproduce themselves by dividing into two illuminated the origin of cells and became a cornerstone of the cell theory.[2553-2555] The fission replication model is the intermediate case between the extremes of a purely auxetic or factory replicator and a purely non-auxetic or unit replicator, a very important and fundamental dimension in the replicator design space. Besides individual cells, some multicellular animals also reproduce by fission. For example, upon reaching a certain size a growing planarian pulls itself in two, after which the head grows a new tail and vice versa, resulting in two smaller individual animals.[679]

Auxetic Replication (replicator expands size of self (auxesis); all replicated components are incorporated into self; factory replicator; unit growth model)

Sequential Semi-auxetic Replication (replicator incorporates replicated components into self, later fissions into two or more identical units; unit fission model)

Non-auxetic Replication (unit replicator copies self at same size; all replicated components are incorporated into daughter device(s); individual replicator; unit duplication model)

I12. Self-Formation Modality. According to Janusonis,[784-786] in self-formation the interaction between the forming object and the chaotic medium (the environment or substrate) is controlled by the forming object's structure, and the structure is changed by the interaction, with the primary object increasing in complexity. Three kinds of self-formation can be used in manufacturing: self-alignment, development, and replication.

Self-Alignment (the object interacts with a distinct sequence of chaotic media)
Development (the object interacts with a single chaotic medium)
Replication (the object generates primary objects)

I13. Replication Process Parallelicity.

Serial Processing (only one process occurs at a time)
Parallel Processing (multiple processes occur simultaneously)
Massively Parallel Processing (most/all processes occur simultaneously)

I14. Replication Process Digitality. Replication based on DNA complementarity is considered digital, whereas autocatalytic cycles are frequently processive (e.g., Section 5.1.4(2)).

Digital Replication (replication proceeds through discontinuous series of distinct, discrete, or modular states)
Replication proceeds via combination of digital and analog processes
Analog Replication (replication proceeds through a continuum of closely-related states; processive; holistic)

I15. Replicator Parts Synthesis. Parts may be fabricated by additive processes, subtractive processes, or by other processes that alter the part without changing the quantity of physical material that is present.

Parts Fabrication primarily via Additive Synthesis (e.g., bulk chemistry, EBID, additive mechanosynthesis (moiety deposition), welding)
Parts Fabrication employs both additive and subtractive synthesis
Parts Fabrication primarily via Subtractive Synthesis (e.g., bulk chemistry, subtractive mechanosynthesis (moiety abstraction), sacrificial lithography, sawing)
Parts Fabrication employs neither additive nor subtractive synthesis (e.g., jig-based parts formation such as injection molding and die casting, and deformation processes such as bending, pressing, etc.)

I16. Number of Distinct Onboard Transformative Processes for Environmentally Available Parts. Edmonds[502] discusses the quantity and variety of transformative operation types in different classes of replicating systems.

Replicator cannot perform any transformative processes on parts available in the substrate
Replicator can perform only one transformative process on parts available in the substrate
Replicator can perform many transformative processes on parts available in the substrate

I17. Ingestor Modality. Physical inputs might not need to cross the replicator boundary if all assembly processes take place external to the replicator, or if the replicator begins operations with all raw materials already contained within its physical boundaries.

Physical inputs enter the replicator continuously
Physical inputs enter the replicator discretely through a gating mechanism
Physical inputs enter the replicator only once during the replication cycle
Physical inputs do not enter the boundary of the replicator

I18. Assembly Process Style. Drexler[208] notes that there are at least two different assembly styles. The first style he calls "construction-style assembly" in which many small devices are used to work on or in a large structure, analogous to constructing a building. Many assembly devices can work in parallel to build up a surface, and the use of larger building blocks can dramatically speed the rate of assembly. Construction-style products can be assembled in poorly controlled environments (i.e., solvent bath), "simplifying problems of heat and mass transport, and of environmental control....Alternatively, eutactic environments of almost any desired size can be constructed by expanding a gas-tight barrier."[208] The second style Drexler calls "manufacturing-style assembly" in which parts and workpieces are manipulated and transported within larger mechanisms — for example, convergent assembly sequences (Section 5.9.4) "in which each structure is built from components within an order of magnitude or so of the structure's own linear dimensions. The motion of components traces a tree in space: the trunk corresponds to the path traced by the final workpiece as the final components are assembled, the branches correspond to the paths traced by those components as they are assembled, and so forth. Convergent assembly can be distributed in space in a manner that (1) provides an assembly volume proportional in size to the workpiece at each stage, and (2) requires only short-range transportation of parts between stages."[208]

Construction-style Assembly (many small assembly devices work in/on a large product structure)
Hybrid-style Assembly (small subproduct structures are assembled inside a single factory device, then have further work performed upon them by many smaller assembly devices; or alternatively, small parts are manufactured by small fabrication devices, then convergently assembled inside a large assembly device)
Manufacturing-style Assembly (many small subproduct structures are worked on inside/upon a large assembly device)

I19. Network Connectivity.

Replicator is connected to the internet or other external communications network
Replicator has intermittent or conditional network connectivity
Replicator has no network connectivity

I20. Audit Trails. Does the replicator log important events (e.g., replication) and register any new replicator it makes with some external agency? Crude analogs in biology are the homeostatic copy number control systems found in plasmids (Section 4.3.5).

Replicator maintains comprehensive audit trails
Replicator maintains selective audit trails
Replicator maintains no audit trails

I21. Process Accounting. Does the replicator require payment of appropriate fees (or analogous transactions) when an item is manufactured (e.g., does it have Digital Rights Management (DRM)[2556] capabilities)?

Replicator has full DRM capabilities
Replicator has limited DRM capabilities
Replicator has no DRM capabilities

I22. Process Security. Does the replicator have effective limits on what it will manufacture? Most importantly, will the replicator only accept and manufacture blueprints that have been digitally signed by some external agency? Or will it manufacture any blueprint you care to download (including illegal drugs, weapons, etc.)?

Replicator has internal limits on what it will manufacture
Replicator has no internal limits on what it will manufacture

I23. Tamper Resistance. Will the replicator resist attempts to physically subvert its security? Does it possess active means (e.g., thermite to insure self-destruction if attacked) to prevent physical subversion of its capabilities? Valuable commercial programs commonly employ either primarily hardware-based locks, such as dongles, or primarily software-based locks, such as authorization codes, to prevent unauthorized usage. (Most hardware-based tamper resistant systems include some software, and vice versa; the issue here is the relative emphasis.) Consider a replicator design which incorporates, say, three major independent architectural means of preventing unwanted replication (e.g., encrypted instruction sets, rare nutrients and broadcast power) along with a nonevolvable design. For such a system, notes Yudkowsky,[2452] "by far the most probable source of serious problems is human abuse, not a point mutation that somehow gets past all three barriers. If a design is resistant to corruption by the space of attacks employed by a human cracker, it will probably be resistant to the space of probable point mutations."

Replicator has both hardware- and software-based tamper resistance
Replicator has either hardware- or software-based tamper resistance
Replicator has no tamper resistance

I24. Reliability of Manufacturing Operations. The normal functioning of the ribosome produces one manufacturing error in 1,000 to 10,000 operations, which limits the size of modules that can be made without some form of error correction mechanism. (Section 4.2; see also L4 "Replication Fidelity"). Errors in fabricated parts are of reduced concern if the parts are to be used in an error-tolerant application or in a noncritical location of a component. For instance, a protein with 1-2 randomly misplaced residues will probably still fold correctly, and some nanomachine parts may work correctly with 1-2 random atoms out of place; but 1-2 misplaced residues in the active site of an enzyme can seriously degrade activity, and 1-2 misplaced atoms at a sliding interface or in a binding site could utterly ruin the performance of nanomachinery.

Manufacturing is of low reliability, allowing the fabrication and assembly of only simple parts and active subunits
Manufacturing is of moderate reliability, allowing the fabrication and assembly of moderately complex parts and active subunits
Manufacturing is of high reliability, allowing the fabrication and assembly of very complex parts and active subunits

I25. Error Correction Mechanisms. Does the replicator include onboard error correction mechanisms (regardless of whether instructions are stored onboard)?

Replicator possesses onboard error correction mechanisms
Replicator possesses no onboard error correction mechanisms

I26. Offspring Separability. Do offspring physically separate from their siblings after they are produced? Lohn and Reggia[371] cite the ability of distinct copies eventually to separate, after being initially adjacent, as a criterion for self-replication in the context of cellular-automata-specific replication. This factor is related to the multicellularity dimension F1.

Offspring remain physically attached to siblings indefinitely after birth
Offspring remain physically attached to siblings for some period of time after birth, but eventually separate after the elapse of some period of time, or the occurrence of specific events
Offspring separate from siblings immediately after birth

J. Replicator Performance

J1. Replication Time. Time required to produce one generation of daughter devices; generation time.

Nanosec 10^{-9}-10^{-6} sec
Microsec 10^{-6}-10^{-3} sec
Millisec 10^{-3}-1 sec
Sec/Min 1-10^{2} sec
Hrs/Days 10^{3}-10^{5} sec
Wks/Months 10^{6}-10^{8} sec
Yrs/Longer $>10^{8}$ sec

J2. Replicator Longevity. Mean time to failure of the parental replicator device. In living organisms, a gene-based biological clock related to telomeres[2557] apparently plays an important role in establishing upper limits to the longevity of individual replicators (organisms).

Nanosec 10^{-9}-10^{-6} sec or less
Microsec 10^{-6}-10^{-3} sec
Millisec 10^{-3}-1 sec
Sec/Min 1-10^{2} sec
Hrs/Days 10^{3}-10^{5} sec
Wks/Months 10^{6}-10^{8} sec
Yrs/Longer $>10^{8}$ sec

J3. Replicator Expiration Date. Providing an expiration date, or a fixed duration of time tallied on an internal counter, after which the replicative function will be permanently disabled[271,2552] can contribute to public safety (Section 5.11). For example, the fictional robots manufactured in the robot factories of Capek's R.U.R.[657] were designed to die after 20 years. In the absence of a clock, a simple pulse counter or copy counter would serve a similar function — after registering some fixed number of input pulses or replication cycles, the counter would automatically sever the power transmission line. But note that most broadcast-architecture replicators need not contain a clock or counter. If all onboard functions are externally powered and controlled, the addition of an onboard stop clock would be a superfluous safety measure, and the replicator could be sent commands to permanently disable itself at any time.

Replicator includes onboard copy counter, pulse counter, or clock used to automatically and permanently disable replicative capacity

Replicator includes no onboard expiration date

J4. Generational and Gestational Fecundity. This is the number of daughters per generation, or per "litter". In biology, in the case of extended-maturation or birth-immature replicators (Section 5.9.1), "generation time" customarily refers to the time required for maturation of an immature replicator — the time required to progress from fertilized egg to adult reproductive maturity — whereas "gestation time" refers to the time required to progress only from fertilized egg to live birth. Note that these replicators tend also to have a relatively small number of litters during a relatively short period of fertility (typically 30 years for human females) so that the number of offspring per generation is not significantly different from the number of offspring per parent (or breeding pair).

In the case of birth-mature replicators (Section 5.9.2), generation time and gestation time are synonymous because there is no post-birth maturation period required. Most proposed artificial replicators, particularly non-auxetic replicators (see I11), and many simple biological replicators such as viruses, bacteria, and other single-celled replicators that follow the eukaryotic cell cycle (Section 4.3.6), are birth-mature replicators whose generation time and gestation time are equivalent, and may be termed the "replication time." Generational fecundity is distinguished from total number of daughter devices per parent device primarily in the case of replicators with unlimited replicative lifespans, wherein generational fecundity can be unlimited (e.g., in immortal cell lines).

In biology, smaller animals generally produce more offspring.[2558] Across the animal kingdom, birth rate falls steadily with increasing food requirements; energy use is closely linked to size, so bigger animals have fewer offspring.[2559] This appeared not to hold for humans, since a 100-kg female gorilla typically has 3-6 offspring while the average North American woman weighs considerably less but will have <2 babies.[2559] But Moses and Brown[2560] found that human birth rates fit the pattern perfectly on the basis of total energy consumption rather than body mass, since the average North American consumes ~11,000 watts including food, transport, heating, entertainment and so on — which would be roughly equivalent to the metabolism of a hypothetical elephant-sized 30,000-kg primate. A further comparison[2560] of contemporary birth rates and energy use in >100 countries and a review of U.S. fertility and energy consumption over the last 150 years confirmed that fertility declines steadily as energy consumption increases.

One daughter device produced per replication cycle (gestational or generational)

Many daughter devices produced per replication cycle (gestational or generational)

J5. Generational Longevity. Refers to the longevity of the line of replicators — that is, can the line of offspring potentially be unlimited? Establishing limits to the maximum number of generations or replication cycles[2561] might enhance public safety of artificial replicators (Section 5.11; see also J3), as already incorporated in biology for other purposes (e.g., telomeres[2557] and menopause[2562]). In the field of cellular automata, Moore[353] required that an entity be capable of causing arbitrarily many offspring in order to be considered "self-reproducing", and Lohn and Reggia[371] also require unbounded growth potential for reproducers in their definition. Of course, restrictions on the total number of generations does not provide a logically complete safeguard against runaway replication unless generational fecundity is also restricted, and vice versa. Meszena and Szathmary[2855] employ a similar measure, called "lifetime reproductive ratio," which is defined as the expected number of offspring of a single replicator during its entire lifespan.

No daughters are produced during replicator lifetime (e.g., auxetic replication only)

One generation of daughters are produced during replicator lifetime

Many generations of daughters are produced during replicator lifetime

Unlimited number of generations of daughters may be produced during replicator lifetime (e.g., immortal cell lines)

J6. Nonreplicator Product Types. Von Neumann originally examined "universal constructors" having the ability to build any design that the instruction tape (genotype) can specify (e.g., automaton "D" mentioned in Section 2.1.1). Cellular automata have been devised that can both self-replicate and construct arbitrary non-self patterns[413] in keeping with von Neumann's original conceptions. However, commercially useful primitive limited-purpose replicators do not need this universality and will be both easier to build and safer to operate if they lack this broad capability. Replication-incompetent viruses have been employed to genetically transform biological cells[2563] and in genetic therapies in medicine.[2564] As our ability to design more general purpose molecular assemblers and nanofactories grows, additional safeguards must be added to these increasingly valuable systems to maintain their status as "inherently safe" (Section 5.11).

Replicator can make no nonreplicator products

Replicator can make a small number of nonreplicator product types

Replicator can make a large number of nonreplicator product types

J7. Qualitative/Quantitative Closure. Measures the ability of the replicator to gain access to all resources needed for replication (Freitas and Gilbreath,[2] Section 5.3.6 and Figure 5.22) and to avoid "production bottlenecks".[1128] (See Section 5.6.) Friedman[19] notes that replication with only partial closure (C) still allows the achievement of quite appreciable production amplications $A = 1 / (1 - C)$, (e.g., $A = 10$-fold amplication for $C = 90\%$), "which is quite valuable for reasonably attainable closures of 90% or more."

One safety concern first raised by Drexler[199] is the possibility that a microscale manufacturing system, once having been engineered to gather resources from natural environments, could, if not controlled, convert biomass on a large scale into a "gray goo" of identical replicators, a process which has more formally been termed "biovorous ecophagy".[2909] In 2004 Drexler[3106] employed the somewhat opaque term "autoproductive" to describe engineered systems that are capable of self-replication but which entirely lack one or more key functionalities for safety reasons — that is, they possess low or 0% closure (Section 5.6) in some important design dimension(s), hence cannot replicate without outside assistance. In the case of replication control autonomy (A1), since at least the 1980 NASA study[2] (Section 3.13) such manufacturing systems have been widely known more descriptively as "teleoperated replicators" (Section 3.13.2), and since the early 1990s this mode of remote control has also been widely known as the "broadcast architecture" (Section 4.11.3.3). One could similarly arrange for 0% parts closure (E4) (aka. the "vitamin architecture"), 0% process energy closure (G1), 0% process manipulation closure (H1), and so forth. As Drexler[3106] reiterates:

> *A set of blacksmith's tools can be used by a blacksmith to make a duplicate set. By themselves, the tools are inert, but with a careful input of skill and muscle they can be used to produce duplicates of themselves. Such a system, which can be replicated but only with substantial outside help, can be called 'autoproductive' to distinguish it from a self-replicating or self-reproducing system. A sufficient condition for the safe use of exponential manufacturing is to use only systems that are autoproductive, but are missing functionality that could make them self-replicating.*

Drexler's choice of the term "autoproductive" was particularly unfortunate because the customary meaning of "auto-" is "self-" or "self-causing," yielding the exact opposite of the meaning intended for the neologism. A more precise term might have been "auxilioproductive," from the two Latin roots meaning, literally, "needing assistance for production."

% of own subunits that replicator can assemble	0%	90%	100%
% of own parts that replicator can fabricate	0%	90%	100%
% of own parts materials that replicator can extract	0%	90%	100%
% of own components that replicator can transport	0%	90%	100%
% of own components that replicator can inspect	0%	90%	100%
% of own components that replicator can warehouse	0%	90%	100%
% of own components that replicator can repair	0%	90%	100%
% of own components that replicator can control	0%	90%	100%
% of own components that replicator can energize	0%	90%	100%

J8. Emission of Waste Products. How much physical waste material does the replicator produce, either during replication or during non-self product manufacturing? The Merkle-Freitas assembler (Section 4.11.3) is the first zero-emissions bottom-up replicator ever proposed — its only effluent is more of its own exterior working fluid — whereas, for example, the Sayama "workplace construction" model[8,9] assumes production of garbage (used workplaces are discarded after self-replication). Some designs may allow temporary sequestration of waste products in onboard caches, which products are then discharged unprocessed as wastes at a time and place well-removed from the time and place where replication or manufacturing takes place. Other designs may provide for internal reprocessing of "wastes" into "products" possessing alternative utility. Zero waste is possible if the replicator uses all inputs in the construction of product. Of course, even in an efficient design some waste heat is inevitable.

Replicator produces mostly waste products
Replicator produces some waste products
Replicator produces zero waste products

K. Product Structure

K1. Product Physicality. See C1 and D1.

Physical Product
Kinematic-Cell Product
Virtual Product

K2. Product Naturalicity.

Wet/Natural (natural, biological, organic, purely biochemical)
Hybrid Wet-Dry or "other"
Dry/Artificial (artificial, nonbiological, mechanical, purely chemical)

K3. Product Technology Level or Granularity. This dimension describes the product feature size, not the overall product size (see K5).

Subatomic ("femtotechnology"?)[2565-2567]
Atomic/Molecular: Nanotechnology (nanoscale)
Microscale: MEMS (microns)
Macroscale: 20th century industrial (mm to meters)
Megascale: Large space systems (km, megameters, etc.)

K4. Product Physical Dimensionality. While it is true that any physical product must have three spatial dimensions, this factor pertains to the number of active or important dimensions. Quantum dots are effectively 0-D products; strands of DNA and many other polymers are effectively 1-D products; and the surfaces of lithographically produced computer chips are effectively 2-D products.

0-D (pointlike)
1-D (linear)
2-D (planar)
3-D (volumetric)

K5. Product Scale.

Subatomic (<0.1 nm)
Nanoscale (0.1-300 nm)
Microscale (0.3-1000 microns)
Macroscale (1 mm -10 m)
Megascale (>10 m)

K6. Product Mass.

Subatomic (<10^{-26} kg)
Nanoscale (10^{-26}-10^{-16} kg)
Microscale (10^{-16}-10^{-6} kg)
Macroscale (10^{-6}-10^{6} kg)
Megascale (>10^{6} kg)

K7. Product Structural Fixity.

Internal components occupy fixed relative structural positions within product boundary
Internal components occupy constrained relative structural positions, but have some freedom of movement relative to each other within product boundary
Internal components occupy no fixed relative structural positions, and are free to move relative to each other within product boundary
Internal components not constrained to remain within product boundary

K8. Product Particity. Is the product composed of discrete parts?

Product is built as a solid block of material without any discrete parts

Product is composed of parts which are all of the same size or type

Product is composed of a convergent sequence of progressively larger parts of uniform sizes and types

Product is composed of a mixture of parts types of various sizes

K9. Product Structural Error Rate. What percentage of the product mass is incorrectly manufactured? One possible metric would be the percentage of mispositioned or mis-selected atoms in the product structure. However, this description is limited to parts with hard-edged error criteria. Some replicators may require parts to be judged on tolerance, not on placement error of atoms.

Product has zero or negligible error in its manufacture

Product has small or modest error in its manufacture

Product has significant error in its manufacture

L. Evolvability

Note that evolvability[2568-2570] (see also Sections 2.1.5 and 5.2) is an undesirable characteristic for artificial replicating systems intended to serve as molecular manufacturing systems (Section 5.11). An important key to suppressing evolvability and the "evolution of diversity"[2571] is to suppress variability — that is, to avoid multigendered systems and to ensure strict replication fidelity. A digital asexual reproductive system, one that only produces the same design generation after generation, can be employed to avoid evolvability. Evolvability must be actively avoided because evolvable hardware, if allowed to progress unchecked, is likely to develop capabilities faster than "centrally-planned machinery," a temptation that runs counter to our desire for strong public safety (Section 5.11).

Smith,[2572] following Eigen and Schuster,[1663] defined three criteria sufficient to consider replicators as "units of evolution": (1) multiplication (replicators give rise to more of the same kind); (2) heredity (like entities produce like offspring); and (3) variability (inexact heredity). Objects of different types having a hereditary difference in fecundity or survival produce evolution in the replicator population via natural selection. But without variability, the replicators are merely "units of selection", and evolution by natural selection cannot occur. Still, we must be cautious. C. Phoenix[572] notes that "even a limited feature set is still susceptible to what one might call physical mutation. For example, a construction error in a robot arm might cause arms that it builds to be more likely to have the same error, even with an unchanged blueprint." Similarly, Yudkowsky[2452] asks: "An important question is whether the replicator design allows for the equivalent of 'prion' disorders — that is, a 'self-replicating' protein misfold that propagates without the need for mutated DNA. For example, suppose that a certain manufacturing defect within a lever arm does not break the lever arm, but reliably results in the same defect being present in any lever arms manufactured with the assistance of the first lever arm. There would then be heritable information between replicators of a type that bypasses the manufacturing instruction streams."

More broadly, Yudkowsky[2452] notes that whether a given design space is evolvable may depend on the probability distribution for mutations, and whether there exists any probable mutation that leaps to a different viable point in the design space: "Has the replicator design been audited to ensure nonevolvability relative to a possible space of probable point mutations?"

L1. Gendericity. The implications of gender in artificial self-replicating machines have only been lightly addressed, even in the realm of cellular automata.[2573] As Merkle[2574] noted in 1989: "In nature, self-replicating systems evolve. A major mechanism supporting this evolution is sex. Even bacteria have sex of a sort (they exchange DNA quite promiscuously). This is a critical component in the ability to evolve. I would therefore suggest that we not include sex in artificially designed self-replicating systems. If there are legitimate research needs for exploring these options, they should be done under tight constraints and should be approached with a great deal of caution." Vitanyi[2573] suggests that a transition from asexual to sexual reproduction is necessary to produce a change in the number and structure of the genetic tapes employed by an organism. A variety of interesting replication-control mechanisms for gendered replicators have been (instructively) explored by nature, as for instance the abortive karyogamy employed by *Wolbachia*,[2575] an endosymbiont rickettsial bacterial species thought to infect the reproductive tissues of up to 20% of all insect species.[2576]

Non-gendered (no data set used during replication)

Mono-gender (1 viable complete data set used during replication)

Fractional-gender (1 viable complete data set commingled with nonlethal data subsets, selected randomly or purposely during replication)

Bi-gender (2 viable complete data sets commingled during replication)

Multi-gender (many viable complete data sets commingled during replication)

L2. Offspring Fertility. Can replicator offspring (i.e., daughter devices) produce further copies of themselves? The "fertility test."

Replicator offspring are never fertile (e.g., replicator produces only "mule" versions)

Replicator offspring are fertile only under specific conditions or in special circumstances

Replicator offspring are always fertile

L3. Number of Fertile Mutant Configurations (aka. "heredity"). Szathmary[2416] notes that autocatalytic replication in the formose system[2419] "is entirely non-informational, there are no hereditary variants." On the other hand, in animal breeding there are a vast number of fertile configurations, allowing breeders to explore a large contiguous phenotypic space — for example, as Mark Tilden notes: "The dog is all the things you can do with a wolf." (Anecdotal evidence claims an increasing incidence of natural births of elephants lacking tusks[2577] and (less likely) of rattlesnakes lacking rattles,[2578] in response to human predation, and the acquired resistance of bacteria to antibiotics is well-known,[2579] though species already at their environmental limits may not be able to adapt to further change).[2580]

In self-replicating robots, a checksum function embedded in the replication program could affirmatively prevent replication of mutant configurations.[2581] (In effect, the checksum serves as an activation key: if the key is incorrect all further construction is halted, or else the system tags itself for disposal or even self-destructs.) An example of active replication data self-policing is found in nature: *Tetrahymena*, a single-celled eukaryote, deletes up to 15% of its somatic nuclear DNA during each replication cycle in a process called "programmed DNA deletion" that can recognize and delete foreign genes that have invaded a chromosome.[2582] This property of replicators is also known as brittleness or "canalization".[2401,2583] It has recently been proposed that an electronic self-test for base pair mutations may occur naturally in DNA that is functionally equivalent to checksum correction.[2584]

Only 1 configuration is fertile; high precision development
A few closely-related mutant configurations are fertile
Many moderately-altered mutant configurations are fertile
Vast number of significantly different mutant configurations are fertile; high tolerance for imprecision

From a pragmatic engineering perspective, it is desirable that small shifts within the design space reliably result in nonviable designs. Notes Yudkowsky.[2452] "All evolved organisms are very highly evolvable by virtue of having evolved. A consciously executed human design tends to leap large areas of design space and contain precise patterns that break easily. Even when minor (probable, point) shifts in the design permit a functionally similar result, the large-scale architecture may still be fragile enough to constrain the design to a particular volume of the design space." Natural biological replicators and artificial replicators designed using evolutionary algorithms are the result of a design process that optimizes by climbing along an incremental pathway composed of exactly the kind of probable point mutations that would be likely to occur in a replicator design that we would prefer to hold constant. Artificial replicators designed using nonevolutionary algorithms are produced by a series of cognitive manipulations that differ fundamentally from the types of point mutations that would be produced by random physical errors, and random physically induced errors in these machines would be unlikely to leap to viable points, let alone to superior points, in the design space.

L4. Replication Fidelity. How faithful is the copy to the original? Luksha[2388] considers the similarity between a producer and what is produced to be a key property of self-reproduction as a general phenomenon. He refers to this dimension as the "parent-progeny relationship" and suggests three classes of self-reproduction including "exact replication," "near replication of an ancestor," and "near replication of a parent." This design factor may be captured by the following unidimensional vector:

Daughter replicators are exact physical duplicates of parent device, to molecular precision
Daughter replicators have minor physical differences from parent device; "difference between each new copy and the original system must be minimal"[2388]
Daughter replicators "imitate the original system, with possible reversible mutations"[2388]
Daughter replicators "must have resemblance with its parent, but not necessarily with all its ancestors (and thus this is a process of irreversible mutations)"[2388]
Daughter replicators may have major physical differences from parent device

In a personal correspondence, Luksha[128] clarifies this analysis by using a two-dimensional grid in which the horizontal axis represents replication fidelity relative to the original replicator and the vertical axis represents replication fidelity to the replicator's immediate ancestor. To quantify fidelity, Luksha introduces a qualitative difference function $d(a,b)$ between an earlier replicator system a and a descendent replicator system b, which is a measure of the distance between the two points a and b in a space of relevant replicator characteristics (e.g., using two such characteristics x and y, then $d(a,b) = \{(x_a - x_b)^2 + (y_a - y_b)^2\}^{1/2}$). Luksha then considers replicator system s_t produced by its immediate ancestor s_{t-1} in generation t, and also some initial system s_0 which starts the reproduction of the given type of systems, where distance D is a level of acceptable variation (e.g., see Eigen et al[2585] for similar measures of this kind used in pre-biotic models). This yields the following two-dimensional classification scheme:

		$v^t_0 = d(s_0, s_t)$		
		$v^t_0 = 0$	$D \geq v^t_0 > 0$	$v^t_0 > D$
$v^t = d(s_{t-1}, s_t)$	$v^t = 0$	exact replica of the original	exact replica of the parent [A]	
	$D \geq v^t > 0$	"reversal" exact replica of the original [B]	near replica of the original	near replica of the parent
	$v^t > D$	not a self-reproduction (production of other system)		

Two cases are only theoretically possible. In case [A], the system has evolved from the original state to some "attractor" state which is reproduced "exactly". "Theoretically, this is a possible case; however, its mechanics are not clear if non-trivial self-replication is considered: a system must conserve its copying to a given structure, but since it has evolved to this structure it has potential for further evolution." Case [B] is another theoretically possible situation where "a system which has evolutionarily 'departed' from a given system occasionally returns to this system."

The effects of copy error on the time evolution[2586] and survival[2587] of simple self-replicating systems have been analyzed by others. Note also that the exact physical duplication at the quantum level is evidently impossible.[276]

L5. Genomic Redundancy. Greater genomic redundancy is believed to contribute to increased evolvability of a replicator[2588] — "populations of robots with larger genotypes achieve systematically higher fitness than populations whose genotypes are smaller." Note that this will not be a consideration in regard to replicators with external non-replicated genomes, such as broadcast-architecture replicators.

Replicators have small, compact internally-stored description, hence minimal genomic redundancy and relatively lower evolvability
Replicators have large, repetitive internally-stored description, hence maximal genomic redundancy and relatively higher evolvability

L6. Environmental Partitioning. Computational studies by Birol et al[2589] show that partitioning of the replicator-accessible environment into two or more homogeneous subenvironments "leads to emergence phenomena exemplified by steady states not obtainable in the equivalent homogeneous system. The coupled environments can host species that would not survive should the coupling be removed. Two coupled environments may have regions in parameter space that result in chaotic behavior, hence segregation in the environment causes complexity in the system dynamics." Hence environmental partitioning may result in greater evolvability (among those classes of replicators capable of mutation), and thus should be avoided when designing stable manufacturing systems. For replicators inherently incapable of mutation, environmental partitioning is not of concern.

Replicators have access only to a single homogenous environment as they replicate
Replicators have access to two coupled homogenous environments as they replicate
Replicators have access to multiple homogenous environments (i.e., a heterogeneous environment) as they replicate

L7. Complexification. “Over the course of biological evolution, new genes are occasionally added to genomes, increasing the complexity of the phenotype. Complexification has led to major innovations in body-plan organization.”[2401] Implementing a mechanism for handling variable length genomes would enable replicator complexification, thus enhancing evolvability in artificial replicators. This should be avoided in “safe replicator” designs. Complexification also is more likely to occur if information caches, parts, or subunits serve multiple unrelated functions (e.g., B12, E9, F7).

New instructions can be added to the replicative instruction set

New instructions cannot be added to the replicative instruction set; fixed-size genomes

L8. Heterochrony. Changes in the timing or ordering of developmental events over generations of replicators is called heterochrony.[2401,2590] In natural (biological) embryogeny, the path to the final product is surprisingly flexible — entire phases of development can be eliminated without sacrificing the end result. “For example, many frog species have evolved away their tadpole stage, yet still grow into mature, sexually functioning frogs.[2591] Their limb buds develop early, and a little frog, rather than a tadpole, ultimately emerges from the egg. Contrariwise, the Mexican axolotl, a salamander, has lost its *adult* stage, and develops mature gonads as a tadpolelike creature.[2592] Their development of gonads has been greatly accelerated so that they become sexually functional as tadpoles. This dramatic flexibility in development suggests that significant modularity underlies the genetic encoding. Because the timing of the development of different modules is so flexible, mutations can safely modify timing, allowing evolution to explore a variety of developmental plans. Heterochrony allows developing components to come into contact with different components, so that evolution can explore many points of synthesis between components....In addition, heterochrony increases the number of successful genotypes by offering a variety of paths to each successful phenotype.... Like Cartesian coordinates being used in lieu of chemical gradients, time itself can be used to regulate genes. Since time is directly available, it can be exploited as a ‘growth hormone’ that explicitly activates and terminates events in embryogeny.”[2401] Similarly, the JohnnyVon replicator simulation (Section 2.2.2) includes a single entity that switches roles over time, changing from genotypic replication in its youth to phenotypic production in its maturity.

Replicator displays heterochrony; may implement mechanisms of timing such as counters, parameters in L-systems, or dynamic regulatory networks.

Replicator does not display heterochrony; includes no mechanisms for changing the timing of events; inflexible development.

L9. Programmability and Learning. Can the replicator respond to, or learn from, the environment, a key component to evolvability? The incorporation of information storage and feedback mechanisms in supramolecular prebiotic assemblies has been called “crossing the Darwinian threshold,” a key step in the origin of life.[1726] A replicator that can be reprogrammed is a simple example of learning from the environment. Safety is reduced when replicators are increasingly able to gather information from more diverse sources in the environment.

Replicator gathers no information

Replicator can be reprogrammed with specific data

Replicator stores information gathered from non-programmed environmental conditions (senses)

L10. Mode of Genomic Heritability. The manner in which self-descriptive information is passed on to offspring determines the modes of evolution that are possible. How, and in what manner, can replicators pass along random-access information to progeny? Safety is reduced when replicators can pass along more versatile memory stores to their offspring.

Replicator passes on no explicit genome to offspring, enabling only environmentally responsiveless random variation

Replicator passes on read-only memory (ROM), without variation (no error or mutation), to offspring

Replicator passes on read-only memory (ROM), possibly with variation (allowing error or mutation), to offspring, enabling Darwinian evolution

Replicator passes on rewritable memory (RAM, or random-access memory) to offspring, enabling Lamarckian evolution

L11. Multilevel Genomic Heritability. Is genomic information heritable only from the level of the whole replicator, or can individual subunits within the replicator pass on heritable information independently of the whole? In regard to metazoan evolution, Hoenigsberg[2593] notes: “The distinction between heritability at the level of the cell lineage and at the level of the individual is crucial. While all out reproduction is the Darwinian measure of success among unicellular organisms, a high replication rate of cell lineages within the organism may be deleterious to the individual as a functional unit. If a harmoniously functioning unit is to evolve, mechanisms must have evolved whereby variants that increase their own replication rate by failing to accept their own somatic duties are controlled. Modifiers of conflict that control cell lineages with conflicting genes and new mutant replication rates that deviate from their somatic duties had to evolve. The metazoan embryo is not immune to this conflict especially with the evolution of set-aside cells and other modes of self-policing modifiers.[2594] In fact, the conflict between the two selection processes permitted a Lamarckian soma-to-germline feedback loop. This new element in metazoan ontogeny became the evolvability of the vertebrate adaptive immune system and life as we know it now. We offer the hypothesis that metazoan evolution solved this ancient conflict by evolving an immunogenetic mechanism that responds with rapid Lamarckian efficiency by retaining the ancient reverse transcriptase enzyme (RNA©DNA) copying discovered by Temin[2595] in 1959 and found in 1970 in RNA tumor viruses by Temin[2596] and Baltimore,[2597] which can produce cDNA from the genome of an RNA virus that infects the cells.” Cell lineage selection within the individual replicator can alter the rate and fixation probability of new mutations.[2598]

Genomic information is not heritable

Genomic information is heritable only at the level of the whole replicator

Genomic information is independently heritable from at least some active subunits of which the replicator is comprised

L12. Interreplicator Information Transfer. Can replicators of different kinds exchange genomic information? In biology, horizontal gene transfer[2599] is the collective name for processes that permit the exchange of DNA among organisms of different species. Replicator safety is enhanced if replicators of different kinds lack the ability to exchange genomic information among themselves.

Replicators of different kinds, or having different genomes, cannot mutually exchange genomic information

Replicators of different kinds, or having different genomes, can mutually exchange genomic information

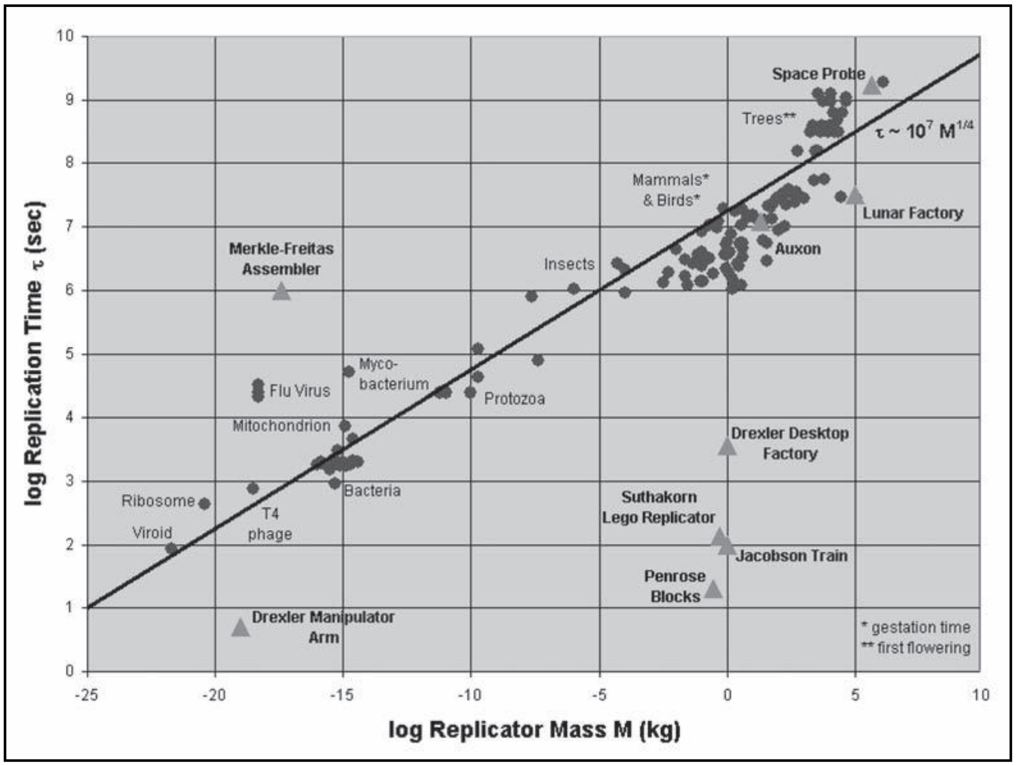


Figure 5.6. The 1/4-power law for replication time as a function of replicator mass, for biological replicators (● = biological replicators, ▲ = manmade replicators).

5.2 Replication Time vs. Replicator Mass

Figure 5.6 shows the replication time (τ) as a function of replicator mass (M) for 126 biological species and 9 actual or proposed artificial kinematic self-replicating systems across a size range spanning nearly 20 orders of magnitude, using data drawn from numerous sources[2600] and tabulated in Appendix A. (The exact formula for the trendline drawn in Figure 5.6 is $\tau = 1.78 \times 10^7 M^{1/4}$.) It is well-known[2601] that the time of fecundity, the age for maturity, and the regeneration time grow with replicator size. For example, as long ago as 1965 Bonner[2602] found a strong nearly-linear positive correlation between body length and the logarithm of generation time. Our data confirm that replication time in biological systems appears to follow a 1/4-power law function of replicator mass, as explained by the model for allometric scaling laws in biology recently proposed by West et al.[2540] Indeed, age at first reproduction can be shown from first principles[2603] to be proportional to $M^{1/4}$, a value which has elsewhere been substantiated empirically.[2604,2605] On the other hand, it is also known that nonfractal mechanical systems such as combustion engines and electric motors exhibit purely geometric 1/3-power, rather than 1/4-power, scaling with mass.[2608-2610] It has been expected that for a given replicator architecture, physical replication speed should be a linear function of geometric dimension (hence a 1/3 power of mass, since mass is volumetric) because nanomanipulator velocity is scale invariant[208] while travel distance decreases linearly with dimension. (See also Section 5.9.5.)

Figure 5.6 may provide one simple answer to a question that is sometimes asked in relation to machine self-replicating systems (SRS):[988] "If self-replication is so easy, where are all the SRSs?" The chart suggests that pre-nanotechnology macroscale replicators may be expected to have comparatively lengthy replication times. For example, the replicating space probe proposed by Freitas (ref. 1014, Section 3.11) was scaled at 4.43×10^5 kg (443 tons) dry mass and a replication time of 1.69×10^9 sec (53.7 yrs), the replicating lunar factory proposed by NASA in the early 1980s (Freitas and Gilbreath,[2] Section 3.13.2) was scaled at a dry mass of 10^5 kg (100 tons) and a replication time of 3.14×10^7 sec (1 yr), and the Lackner-Wendt auxons (Section 3.15) were scaled to a ~20 kg mass and $\sim 1.2 \times 10^7$ sec replication time.[1128] All lie close to the $M^{1/4}$ trendline and suggest that autonomous meter-sized (or larger) replicators that do not make use of nanoscale manufacturing technologies may have replication times on the order of months or years. Solid printers (Section 3.20) typically weigh 200-500 kg with an effective "replication" time of 1-3 months (about 1 order of magnitude below trendline). The replication time of a typical modern industrial park or machine shop may also be on the order of months to a year, so to obtain a millionfold expansion of factory mass one must wait ~20 replication cycles (i.e., $2^{20} \sim 10^6$), or ~2-20 years. The conventional economics of discounted present value, plant depreciation, and 3-5 year venture capital investment horizons would render most such projects commercially nonviable. Investing today in a seed device that one must pay skilled people to teleoperate for 2-20 years during the non-productive growth phase, yielding at the end of that time a 2-20 year old, possibly nearly obsolete, factory makes little economic sense.

However, using nanotechnology-based replicators having replication times on the order of 1000 seconds allows a millionfold capacity increase in only 200,000 sec (~2.5 days) — that is, rapid prototyping, fast factory buildout, and quick movement to market with useful products made in a nonobsolete manufacturing facility. The scaling laws for replication speed as a function of replicator size thus appear to interact with the economic and obsolescence factors to produce a viable scenario for the deployment of commercial replicators only in the microscale, but not in the macroscale, realm.

Because biological replication time scales as $M^{1/4}$, larger replicators must spend a longer absolute time accumulating resources and maturing tissues than do smaller replicators.[2611] Additionally, in biology a smaller individual replicator produces a mass of offspring that represents a larger fraction of its adult mass than a larger replicator,[2611] and smaller animals generally produce more offspring[2558] — further facts which argue for the comparatively greater commercial value of microscale manufacturing systems that offer rapid ramp-up of output capacity and higher production per unit mass of factory machinery.

Consider a replicator of mass M that produces a mass of offspring $M_{off} = \lambda M$ that is some fraction λ of its adult mass. M_{off} has been empirically shown[2604] to scale approximately as $M^{3/4}$ in biological systems, and "from first principles it can be argued that when reproduction begins, the amount of reproductive biomass accumulated will be proportional to the amount of energy intake".[2603] Hence λ, the proportion of a replicator's mass that its offspring represents at birth, must be proportional to $M^{-1/4}$. Maurer[2611] notes that "if we compare large and small species within a taxon, in general, we would expect that reproduction in the largest species will be constrained by the longer times it takes to reach reproductive maturity, and the proportionately smaller mass of offspring that can be produced. It is important to recognize that these two allometric constraints on reproduction arise from the energetic processes that underlie organismal growth, given that the organism is constructed of tissues organized into fractal-like networks for the distribution of energy and matter — the fundamental insight implicit in the controversial concept of reproductive power[2612-2617] defined as the rate of production of reproductive biomass."[2613] Whether these same allometric scaling laws that apply to fractal biological systems also apply to artificial mechanical replicators remains to be fully investigated.

As further points of interest, several additional artificial mechanical replicators are shown on Figure 5.6 — including (among others) one which remains, at present, only theoretical (the Merkle-Freitas assembler; Section 4.11.3), and another which has already been demonstrated experimentally (the Suthakorn LEGO® replicator; Section 3.23). By the bio-centric measure of this data, the Merkle-Freitas assembler appears very inefficient and seems to require at least 3 orders of magnitude potential improvement in replication speed to catch up with biological systems. Even with this handicap, the device still replicates at least an order of magnitude faster than conventional macroscale industrial machinery. But replication time is not merely a function of mass, as indicated by the seemingly anomalously rapid replication time achieved by the comparatively simple Suthakorn-Chirikjian LEGO® replicator. Replication time is also a function of the complexity of the device, the replicator parts count or parts size, the degree to which the replicator must fabricate components from a disordered feedstock, the degree to which control and processing mechanisms can be offloaded from the replicator device to external systems, and potentially dozens of other dimensions of the replicator design space (Section 5.1.9). It is possible, even likely, that nanotechnology-based replicators can be at least 1-2 orders of magnitude more efficient than biological replicators, size for size, albeit at the cost of higher power density (*Nanomedicine*,[228] Section 6.5). But until comprehensive further studies can elucidate the precise scaling laws governing the replication time of mechanical replicators, natural biological systems may stand as useful benchmarks of the minimum performance that may be expected from future artificial self-replicating systems.

Finally, note also that evolvability scales inversely with size, all else equal. In the first place, in biology the replicator abundance increases as a function of decreasing replicator size,[2618-2623] with the number of replicators N(m) as a function of replicator mass m given by $N(m) \sim \text{constant} \cdot m^{-2}$, a Zipf power law distribution believed due to predation-related deaths in macroscale animals.[2624] In the second place, the number of distinct (biological) replicator species is a declining function of the characteristic size of individual species members — i.e., smaller creatures produce more species,[2606-2608] as illustrated by the frequency distribution of both insect and vertebrate species count as a function of organism body length compiled by Pianka[2625] and as a function of body mass for 2104 mammals compiled by Maurer.[2611] More specifically: There are ~10^5 known species[2626] of mammals, birds, reptiles, amphibians, fishes and mollusks, of characteristic individual organism mass ~0.1 kg, with, for instance, an estimated ~3×10^{11} birds alive on Earth.[2627] There are 751,000 (i.e., ~10^6) known species[2626] of insects (estimated up to ~3×10^7 species counting currently unknown insect species[2628]) of characteristic individual organism mass ~10^{-5} kg, with an estimated ~10^{19} individual insect organisms alive on Earth.[2629-2631] As for bacteria, microbial systematics is still in its infancy and fewer than 5000 bacterial species have been formally described,[2626,2632] in part because of the traditional difficulty of distinguishing bacterial species in optical microscopes. But modern measurements using molecular biology techniques have found ~4000 different bacterial species in a mere 1 gm of Norwegian forest soil[2633] and Sugawara et al[2634] have identified 334,312 distinct strains of bacteria that are already known. Even traditional conservative estimates[2635-2637] put the total number of unknown bacterial and fungal species at ~10^7 but the most recent estimate[2638] is that the unknown bacterial species count could plausibly reach as high as ~10^8-10^{13} species, with an estimated ~10^{31} individual bacterial organisms of characteristic individual organism mass ~10^{-15} kg currently alive on Earth.[2639] These limited data tentatively suggest a coarse trendline species count of $N_{species}(m) \sim 10^5\ m^{-1/2}$.

The concern here is that, for a given machine architecture, the smaller the device, the faster that unit reproduction may occur, and hence the greater the number of trial offspring that the device could sire (and test for fitness) per unit time interval. Macroscale reproducers that generate variability only via stochastic genomic mutations are far less likely to be able to generate enough trial offspring to stumble upon successful new phenotypes in any reasonable period of time. Microscale reproducers, on the other hand, may be able to generate offspring up to a million times faster, thus could be far more likely to randomly yield productive modifications, hence to "evolve," if their design foolishly permits such viable modifications. Microscale replicators may therefore be viewed as inherently more risky from a public safety standpoint[199,2909] and so the need for adherence to design guidelines[271] to forestall unplanned system evolution is more urgent in this realm.

5.3 Minimum and Maximum Size of Kinematic Replicators

What is the minimum size for free-standing autonomous kinematic replicators? In microbiology, this question has been tentatively addressed in the past,* with the conclusion that the theoretically smallest biological cells that can be contained within a membrane must have diameters of at least ~50 nm[1774] to 140 nm.[1866,2640] This question has more recently been analyzed in depth by a special panel of nearly two dozen researchers at a workshop entitled "Size Limits of Very Small Microorganisms," sponsored by the Space Studies Board of the National Academy of Sciences and first published in 1999.[2641,2642] This study was motivated in part by the announcement[2643] of possible evidence for relic biogenic activity in the Martian meteorite ALH84001. This evidence included an observation of "carbonate globules and features resembling terrestrial microorganisms, terrestrial biogenic carbonate structures, or microfossils" that ranged in length from 10-200 nm as revealed in electron microscope images, and also other evidence for nanometer-scale

---

** In the 1960s, NASA sponsored research[2662] to inform future astronauts how to recognize even the most rudimentary forms of life on other worlds — with the conclusion that the simplest living thing would contain at least 124 proteins of 400 amino acids each, and would possess a functioning genetic code so the organism would reproduce true to type.*

biomineralization and "nanofossils" on Earth[2644-2646] — even though exotic morphological forms resembling biogenic structures can occur via nonbiological processes,[2647] and many bacteria are known to undergo transition from a large active state to a small dormant state,[2648-2650] often in response to starvation.[2648] The study also was motivated by reports[2653-2660] of "nanobacteria" with calcium shells which have been proposed as possible nucleation sites for kidney stones.[2655-2657] Some of these microbes are claimed to be cultured from blood[2653,2654] and apparently have diameters as low as 80 nm but average 200 nm (mass ~ 4 x 10^{-18} kg, replication time ~3 days ~2.6 x 10^5 sec[2520]). There are also reports of "nannobacteria" as small as 30 nm in diameter present in everything from tapwater to tooth enamel[2661] and "ultramicrobacteria"[2650-2652] with cell volumes of 0.03-0.08 μm^3 (386-535 nm spherical diameter).[2651]

Within the NAS Workshop,[2641] geneticists and cell biologists "reached consensus on the smallest size likely to be attained by organisms of modern biochemical complexity. Free-living organisms require a minimum of 250 to 450 proteins along with the genes and ribosomes necessary for their synthesis. A sphere capable of holding this minimal molecular complement would be 250 to 300 nm in diameter, including its bounding membrane. Given the uncertainties inherent in this estimate, the panel agreed that 250 ± 50 nm constitutes a reasonable lower size limit for life as we know it. At this minute size, membranes have sufficient biophysical integrity to contain interior structures without the need for a cell wall, but only if the organism is spherical and has an osmotic pressure not much above that of its environment. Bacteria with a diameter of 300 to 500 nm are common in oligotrophic (nutrient-poor) environments, but smaller cells are not. Nanobacteria (a single-celled microorganism proposed to have a maximum diameter in the range of tens to a few hundreds of nanometers) reported from human and cow blood fall near the lower size limit suggested by cell biologists. However, the much smaller (ca. 50 nm) bodies found in association with these cells may not, themselves, be viable organisms. Observations on Archaea indicate that, in general, they have size limits similar to those for Bacteria. Whereas a cell operating by known molecular rules — with DNA or maybe RNA, ribosomes, protein catalysts, and other conventional cell machinery — would have a lower size limit of 200 to 300 nm in diameter, primitive microorganisms based on a single-polymer system could be as small as a sphere 50 nm in diameter. On Mars or Europa, fossils might preserve a record of biological systems different from those we understand — perhaps early products of evolution that made do with a small complement of functional molecules. Organisms of modern biochemistry might become small by being pathogens or living in consortia — that is, by using the products of another organism's genes."

NAS Workshop participant and biochemist Michael Adams[2524] calculated that a 50 nm diameter spherical cell would just have enough room for 2 ribosomes, 520 30-kDa proteins, and 8 1000-bp genes as DNA — well below the minimum possible genome size of ~250 genes[1866,1867] which would still require the cell to be parasitic, relying on ready-made nutrients from the external environment or a host.[2642] Even *Mycoplasma genitalium*, the free-living microorganism with the smallest known genome (Table 5.1), has 471 genes[1867] that occupy 10% of cell volume.[2641] So 50 nm is likely too small, concluded Adams:[2524] "...the minimum theoretical size for a cell is 172 nm diameter. To grow, such a cell must be supplied with (and must assimilate) all amino acids, fatty acids, nucleotides, cofactors, etc., because it would contain the minimum number of genes (250) and have a minimal biosynthetic capacity. The [172 nm] cell would have a 5 nm membrane but no cell wall. It would consist, by volume, of 10% DNA, 10% ribosomes, 20% protein, and 50% water, and would contain approximately 65 proteins per gene as well as 65 ribosomes." By positing a reduced protein size and shifting to single-stranded DNA and segmental genome copying, biophysical chemist Peter Moore[2663] argues that a 60-nm living cell might be possible but must "invoke a biochemistry unlike any known in modern cellular life. A cell that is even smaller would require even more radical departures....their biochemistry will be a lot different from anything we know today."

For example, Benner[2664] noted that "much of the volume of a bacterial cell is filled with machinery (ribosomes) that convert information in the genetic biopolymer (DNA) into information in the catalytic biopolymer (protein). This places a limit on the size of a two-biopolymer living system that all but certainly excludes cells as small as (for example) the structures observed in the Allan Hills meteorite derived from Mars. Life that uses a single biopolymer to play *both* genetic and catalytic roles[2665-2671] could conceivably fit within a smaller cell." Benner suggested that a single-biopolymer system could be packed into a 50-nm sphere. However, he admitted, "no biopolymer has yet been found that can play both roles, and the chemical demands for genetics and catalysis are frequently contradictory."

A bottom-up biochemical analysis of the minimum requirements for the first primitive lifeform on Earth by Ferris[2672] suggested that if it was possible to have membrane-bounded nonribosomal life with a minimum of five genes (i.e., ligase, replicase, monomer synthase, fatty acid synthase, and membrane synthase ribozymes), then if the organism achieved the single-stranded RNA packing density of Qβ virus it would need an interior volume of 3,580-nm^3 plus the volume of the surrounding membrane, giving a spherical outside diameter of 27 nm assuming a 4 nm thick membrane. If instead the earliest organism achieved only the double-stranded RNA packing density and protein/biomolecular content typical of contemporary L-A virus, then one would need an interior volume of 48,900-nm^3, giving a spherical outside diameter of 53 nm again assuming a 4 nm thick membrane.

Alternatively, NAS Workshop participant Jeffrey Lawrence[2497] hypothesized the possible existence of very tiny self-replicating "cells" based on sequential horizontal transfer of single genes "wandering" among a consortium, illustrating that not all cells need have all the essential genetic information at the same time: "A model is presented whereby the frequency of gene exchange is much greater than the frequency of cell division. In this model, cells may be considered way stations for gene replication and transfer; such organisms need not maintain a full complement of genes, and genome sizes may decrease." Replication would be very slow (e.g., 10,000 times slower than bacteria, as posited for nanobacteria[2520]) and dependent on the lifetime of biosynthetic intermediates and on the rate of gene transfer, but simulations by Lawrence[2497] predicted "the propagation of organisms where the average cell contains, on average over time, fewer than 1 gene." Using this strategy, a ~50 nm cell barely large enough to hold 1-2 ribosomes might become feasible. However, another study[2641] participant noted that there could be great selective advantage of aggregating more than one gene into a single compartment by cell-cell fusion, so that even starting with the minimal mechanically stable vesicle size, the system would tend to evolve to larger, more efficient compartments. The greater surface area to volume ratio of smaller cells has been claimed to be adaptive for low-nutrient environments,[2673] though counterexamples exist.[2674] In the search for the great universal ancestor of all life, Woese[2675] notes that if there was a great deal of gene transfer, the whole question of the identity of the first cell may become meaningless because the "universal ancestor" of all terrestrial life may not have been one cell, but rather the "genetic annealing"[2675] of a "primordial commune"[2924] of protocells, or as Cowen[2676] describes it, "a kind of cellular mist in which genes transfer from one droplet to the other like molecules of water vapor." Rasmussen et al[1959] suggest a specific design for a simple protocell capable of self-replicative cycling.

The absolute minimum possible size of purely mechanical (nonbiological) kinematic replicators has not yet been seriously addressed by nanotechnology theorists, but it seems unlikely that a fully autonomous mechanical replicator can be significantly smaller than the ~100 nm size range. However, just as the ~25 nm ribosome is much smaller than the smallest known well-documented free-standing biological cell, it is conceivable that remotely powered and fully-teleoperated nanomechanical manipulators capable of assembling themselves from a handful of prefabricated parts using one or a few simple mechanical processes might be possible at the ~10-20 nm scale. Future research will doubtless clarify this point. Using the replication time/mass relation shown in Figure 5.6, a 20-nm teleoperated replicator with normal density could have $\tau \sim 200$ sec.*

The maximum possible size of a kinematic replicator is presently unknown, but is likely extraordinarily large. Consider the purely speculative possibility of audaciously extrapolating the known relationship between replication time and replicator mass shown in Figure 5.6 by another 7 orders of magnitude, beyond the current 10 orders of magnitude in time for which we already have extensive real-world replicator data. If the maximum possible replication time approximates the current estimated age of the universe, or $\tau \sim 1.37 \times 10^{10}$ years ($= 4.30 \times 10^{17}$ sec),[2677] then from the empirically observed relation $\tau \sim 1.78 \times 10^{8}\, M^{1/4}$ (Section 5.2) we would compute that the largest possible replicator that could demonstrably exist (i.e., having executed at least one full replicative cycle) would have a mass of $M \sim 3.4 \times 10^{41}$ kg, or about one-third of the mass of our own Milky Way galaxy (~9.8×10^{41} kg, including ~400 billion visible stars and ~4.9×10^{11} solar masses).[2678] Information/materials traveling at/near the speed of light ($c = 3 \times 10^{8}$ m/sec) can make $N_{Rt} \sim c\,\tau \,/\, D_{repl}$ round trips across a replicator of diameter D_{repl}. If the mass is distributed throughout a galaxy-sized replicator with $D_{repl} \sim 100{,}000$ light-years, then $\mathbf{N_{Rt} \sim 10^{5}}$. If the mass is concentrated in a replicator approaching maximum possible density (i.e., within the Schwarzschild radius of a nonrotating uncharged black hole), then $D_{repl} \sim 4\,GM/c^{2} \sim 10^{15}$ meters (taking gravitational constant $G = 6.67 \times 10^{-11}$ N-m^{2}/kg^{2}) and so $\mathbf{N_{Rt} \sim 10^{11}}$. For comparison, a human body with a replication time of $\tau = 0.736$ year (~9 months) and a bloodstream circulation time of ~1 minute[228] (using fluidic/chemical information transport at <1 m/sec) has an effective $\mathbf{N_{Rt} \sim 10^{6}}$.

5.4 Efficient Replicator Scaling Conjecture

The first simple molecular assembler is likely to be a macroscale device, perhaps a modified SPM system as was being pursued by Zyvex starting in 1998 (Section 4.14). Multiple SPM heads could be equipped with a small number of nanoscale tool tips. In some scenarios, nanoparts fabricated using either bulk chemistry or positional mechanosynthesis techniques would be inspected and selected by the SPM, then assembled one by one into working nanomachines (e.g., the desired useful nanoscale products). Such assembly operations will be very slow, because the placement of each new component may require simultaneous rotations and translations of large macroscale SPM components. Assembly time may scale roughly linearly with assembler size[208] because smaller assembler components moving at a given velocity need to travel less distance to accomplish a given physical operation, consuming less time and energy per physical operation. Hence an important early developmental goal would then be to design and fabricate nanoscale molecular assemblers whose manipulatory components are closer in size to the scale of the parts which must be assembled.

In 1996, Freitas[2679] informally proposed the "Efficient Replicator Scaling Conjecture" which holds that "the most efficient replicator will operate on a substrate consisting of parts that are approximately of the same size scale as the parts with which it is itself constructed. Hence a robot made of ~1 cm parts will operate most efficiently in an environment in which ~cm-scale parts (of appropriate types) are presented to it for assembly. Such a robot would be less efficient if it was forced to build itself out of millimeter or micron-scale parts, since the robot would have to preassemble these smaller parts into the 1-cm parts it needed for the final assembly process. Similarly, input parts much larger than 1 cm would have to be disassembled or milled down to the proper size before they could be used, consuming additional time, information, and physical resources — also reducing replicative efficiency. If this conjecture is correct, then it follows that to most efficiently replicate from an atomic or molecular substrate, you would want to use atomic or molecular-scale parts — that is, nanotechnology."

This conjecture seems broadly consistent with Drexler's scaling analysis of an exemplar manufacturing system architecture using 10 stages of convergent assembly in which product scale is commensurate with mechanism scale at all but the earliest stages of input ordering and reagent preparation involving simple molecular inputs (*Nanosystems*,[208] Table 14.1; see also Section 4.9.3). It also seems consistent with Merkle's analysis of the convergent assembly approach to molecular manufacturing (Section 5.9.4) using a progression of manufacturing stages at different scales.[213] As Fearing[1581] noted in connection with the efficient construction of microdevices: "There are many advantages to shrinking robots and mechanical actuators to the same size as the parts to be manipulated....."

5.5 Fallacy of the Substrate

To generate macroscopic quantities of useful products using nanoscale manufacturing systems, huge numbers of such systems must join in the work. Building a huge number of microscopic systems one by one is time-prohibitive, hence the concept of massively parallel assembly or self-replication is key to all known proposals for rapid molecular manufacturing (Section 5.7). As conceived by von Neumann (Section 2.1.2) and subsequent researchers, the most general theoretical conception of physical replication views replication as a manufacturing process. In this process, a stream of inputs enters the manufacturing device. A different stream of outputs exits the manufacturing device. When the stream of outputs is specified to be identical to the physical structure of the manufacturing device, the manufacturing device is said to be "self-replicating."

Note that there are no restrictions of any kind placed upon the nature of the material inputs. On the one hand, these inputs could consist of a hot plasma containing equal numbers of atoms of all 92 natural elements — which is by some measures a "perfectly random" input stream. On the other hand, the material input stream could consist of cubic-centimeter blocks of pure elements. Or the stream could consist of prerolled bars, sheets, and wires, or more ordered inputs such as pre-formed gears, ratchets, levers and clips. Or the inputs could consist of more highly refined components* such as pre-fabricated whole motors, switches, gearboxes, and computer chips. A manufacturing device that accepts any of these input streams, and subsequently outputs precise physical copies of itself, clearly is "self-replicating." Insisting that only assembly of a copy starting from highly disordered substrates like a hot random-atom plasma or even a somewhat more ordered natural free-range environment counts as "true" replication[988] is one manifestation of the Fallacy of the Substrate. In fact, construction of self-structure from *any* stream of inputs, however ordered or disordered, properly may be termed self-replication. Stated more succinctly, the Fallacy of the Substrate is the assertion that replication, or replicators, can be described or defined without reference to their input substrate. To ignore the substrate upon which replication will take place is to perpetrate the Fallacy.

---

* *The same time/mass relation would predict a replication time of $\tau = 3.6$ sec for a replicator having the limit mass of a single proton, neutron, or hydrogen atom (or $\tau = 0.55$ sec for a single-electron-mass replicator) that could somehow replicate solely by the manipulation of covalent bonds and other conventional interatomic forces. But self-replicating entities that employ nuclear forces can replicate much faster and thus are not represented by Figure 5.6. Neutrons are one well-known example of such a nuclear replicator: a single thermal neutron, upon entering a substrate consisting of a ${}_{92}U^{235}$ nucleus, induces fission of that nucleus in ~10^{-12} sec, replicating 2-3 daughter neutrons which are emitted from the substrate along with various larger fissile fragments, leading to a macroscopic chain reaction if a critical mass of substrate is present.*[2987]

The 1980 NASA study on replicating systems[2] offered an amusing illustration of the Fallacy of the Substrate with its example of a self-replicating PUMA robot. This robot was conceptualized as a complete mechanical device, plus a fuse that must be inserted into the robot to make it functional. Here the input substrate consists of two distinct streams: (1) a stream of 99.99%-complete robots arriving on one conveyor belt, to the left, and (2) a stream of fuses arriving on a second conveyor belt, to the right. The active replicator robot combines these two materials input streams, and the result of this manufacturing process is a single output stream consisting of physical duplicates of itself. Undeniably, the robot has "replicated." Similar two-component replication schemes are commonplace in simple self-replicating chemical systems[1372] of the form $A + B \rightarrow T$, where A and B are substrates that bind to a complementary template T and become joined to form a product molecule that is identical to the template,[1373-1376] i.e., $AB = T$.

In principle, different replicator motifs might metabolize any of an infinite number of input substrates. Depending upon its design, a particular replicator device may be restricted to replication from only a very limited range of input substrates. Another replicator device may have sufficient generality to be able to replicate itself from a very broad range of input substrates. In some sense this generality is a measure of the device's survivability in diverse environments, and may contribute to its self-replicability (Section 5.1.9 (C11)) and evolvability (an undesirable trait in a manufacturing system; Section 5.1.9 (L)). But it is clearly fallacious to insist that "replication" can occur only when duplication of the original manufacturing device takes place from some highly-disordered, ill-defined or arbitrary substrate.

Of course, as a practical matter the economic value of replication is best realized when the substrate is inexpensive. The input stream of 99.99%-complete robots might prove expensive to make in the absence of some prior manufacturing step able to operate on a less expensive substrate.

Replicating systems may be very simple. Von Neumann concluded that kinematic machine replication was possible and that perhaps twelve different kinds of subunits of unknown complexity might be required as building materials. Falling prey to the Fallacy of the Substrate, Haldane[2680] subsequently inferred that as many as $\sim 10^5$ parts might be needed to make a replicator. This inference was refuted just three years later with the arrival of the first in a series of ingenious designs for mechanical self-replicating machines that were built and operated or designed in the late 1950s (Sections 3.3-3.5), composed of no more than about a dozen parts that were made readily available in the external environment and were assembled into a complete (and fertile) daughter machine by the parent machine. Replication is fundamentally so simple a task that artificial machines capable of displaying this behavior in primitive form pre-date most of the modern electronic computer era. Analogizing from results in cellular automata replication studies, James Reggia[402] notes: "Self-replication is not an inherently complex phenomenon but rather an emergent property arising from local interactions in systems that can be much simpler than is generally believed."

Perhaps the most important message of the Fallacy of the Substrate is that the replicative capacity of a replicator cannot be defined by specifying the replicator in isolation from its surroundings. Replicative capacity can only be defined by simultaneously specifying *both* the replicator *and* the input substrate upon which the replicator will be required to operate. This requirement is well-known in biology, where DNA, while representing the "recipe" of an organism and thus information about the replicator's own structure, more importantly represents a plan for how to build an organism that can best survive in its native environment and pass on that information to its progeny.[504] Deutsch[2681] refers to this view as: "genes embody knowledge about their niches." In cell biology the replicative environment can be extremely complex, consisting of the ribosomes which translate mRNA-based genetic messages, an abundance of nutrients inside and outside of the cell, the environment of the organism proper (e.g., ambient temperature and oxygen in the air), and so forth. As Adami[504] explains: "An organism's DNA is not only a 'book' about the organism, but is also a book about the environment it lives in, including the species it co-evolves with. Accordingly, *Mycoplasma mycoides* (which causes pneumonia-like respiratory illnesses) has a complexity of somewhat less than one million base pairs in our nasal passages, but close to zero complexity most everywhere else, because it cannot survive in any other environment — meaning its genome does not correspond to anything there."

A dramatic demonstration of this now-obvious truth was provided by Sol Spiegelman, an American microbiologist who in the mid-1960s posed the deceptively simple question: What is the smallest molecule capable of replicating itself? In Spiegelman's classic experiment,[2682] a primitive phage $Q\beta$ virus consisting of a single 4500-nucleotide RNA molecule was supplied with an abundance of replicase enzyme (the viral enzyme that duplicates RNA) and free nucleotides that the virus needed for replication and survival, in a test tube using a flowthrough system that continually added the nutrients. With the provision of these materials, the virus was no longer dependent upon a cell to continue its life cycle and began to compete against itself, improving the efficiency of replication through the evolution and survival of viruses that did not produce the supplied materials. Within seventy generations, rapidly reproducing mutant strands having only 220 nucleotides had replaced all other variants. The successful mutants had neither viral coats nor the ability to produce the replicase enzyme, and represented a specialized new creature adapted to its whole environment, including the biotic and abiotic components. The replicating RNA had shrunk to the minimum size of the supplied replicase enzyme's recognition site. (Had the RNA shrunk any smaller, it would not have been able to use the free replicase, and thus to achieve closure it would have to have either made its own replicase or invented a jig that would permit use of the existing replicase. This would be very difficult because losing nonessential components is far easier than evolving new structures through mutation, hence the size of the replicase site acts as a closure attractor.) Although the mutant molecule could reproduce itself at a fantastic rate in the protected test tube environment, it could not survive in the unprotected natural world where the input substrate was no longer ideal. Its replicative capacity had become permanently diminished in, and uniquely dependent upon, the new richer substrate.

---

* *The nutritional requirements of the self-replicating machines described in Sladek's 1968 novel* The Reproductive System[672] *clearly violate the safety recommendations of the Foresight Guidelines[271] — guidelines which we endorse (Section 5.11). Sladek writes:*

"During the week...the boxes had devoured over a ton of scrap metal, as well as a dozen oscilloscopes with attached signal generators, thirty-odd test sets, desk calculators both mechanical and electronic, a pair of scissors, an uncountable number of bottle caps, paper clips, coffee spoons and staples (for the lab and office staff liked feeding their new pet), dozens of surplus walky-talky storage batteries and a small gasoline-driven generator.

"The cells had multiplied — better than double their original number — and had grown to various sizes, ranging from shoeboxes and attaché cases to steamer trunk proportions. They now reproduced constantly but slowly, in various fashions. One steamer trunk emitted, every five or ten minutes, a pair of tiny boxes the size of 3x5 card files. Another box, of extraordinary length, seemed to be slowly sawing itself in half.

"General Grawk remained unimpressed. 'What does it do for an encore?' he growled...."

Concludes Luksha and Plekhanov:[2683] "It is evident that any information may only exist relative to (or in relation with) a complex system that processes it (self-replicators in particular); this may be generalized as a principle of information relativity."

5.6 Closure Theory and Closure Engineering

Fundamental to the problem of designing self-replicating systems is the issue of closure. In its broadest sense, this issue reduces to the following question: Does replicating system *function* (e.g., factory output) equal or exceed system *structure* (e.g., factory components or input needs)? If the answer is negative, the system cannot independently fully replicate itself; if positive, such autonomous self-replication may be possible.

Consider, for example, the problem of parts closure. Imagine that the entire factory and all of its machines are broken down into their component parts. If the original factory cannot fabricate every one of these items, then parts closure does not exist and the factory is not fully self-replicating. For replicating machine systems, 100% closure is theoretically quite plausible — no fundamental or logical impossibilities have yet been identified.* The theoretical capability of machines to perform "universal computation" and "universal construction" can be demonstrated with mathematical rigor,[3,310] so parts assembly closure is theoretically possible. And at least in the case of human-operated factory systems, notes Friedman,[20] "we have an existence proof: The set of all factories in the United States can produce useful products and they — as a system — clearly have the ability to produce more of their own kind (or where else did they come from?)."**

In an arbitrary system there are three basic requirements to achieve closure:

1. **Matter closure** — can the system manipulate matter in all ways necessary for complete self-construction? As previously noted, the U.S. factory manufacturing system constitutes an existence proof that 100% materials (and energy) closure is possible.
2. **Energy closure** — can the system generate sufficient energy in the proper forms to power the processes of self-construction?
3. **Information closure** — can the system successfully command and control all processes required for complete self-construction? The vast proliferation of tens of thousands of different species of fully-autonomous self-replicating internet viruses and countless autonomous virtual organisms and artificial life software entities (Section 2.2) constitutes an existence proof that 100% information closure is possible in artificial self-replicating entities. The information caches needed to describe self-replicating systems can be surprisingly modest, often $<10^6$ bits (Table 5.1).

Moore[677] nearly anticipated closure engineering. Describing the required design effort for "artificial living plants" in his 1956 article, he wrote: "Once the list of needed materials was chosen, engineers would have to design a flow scheme for the automatic manufacture of all of them. It would be very desirable to keep the list of materials as short as possible, and the manufacturing operations and processes as simple as possible." During 1979-1980, Freitas[1014] attempted the first quantitative closure analysis for a proposed self-replicating machine system, with special attention to materials, structural, and functional closure issues. Concentrating on materials closure, Freitas performed a scaling analysis of a replicator with reference to the chemical elements required to build the replicator structure as compared to the element availability in the external environment in which the replicator would be expected to operate (Section 3.11).

The 1980 NASA study of self-replicating lunar factories (Section 3.13), co-edited by Freitas,[2] included a similar quantitative analysis of lunar factory elemental composition as compared to the elemental composition of lunar regolith which would be the source of the materials to build the factory. Equally importantly, the NASA study also introduced the concept of systematic closure engineering, describing qualitative closure (can all parts be made?), quantitative closure (can enough parts be made?), and throughput closure (can parts be made fast enough?), and providing a crude qualitative methodology for seeking and achieving closure in all of its many dimensions (Figure 5.7).

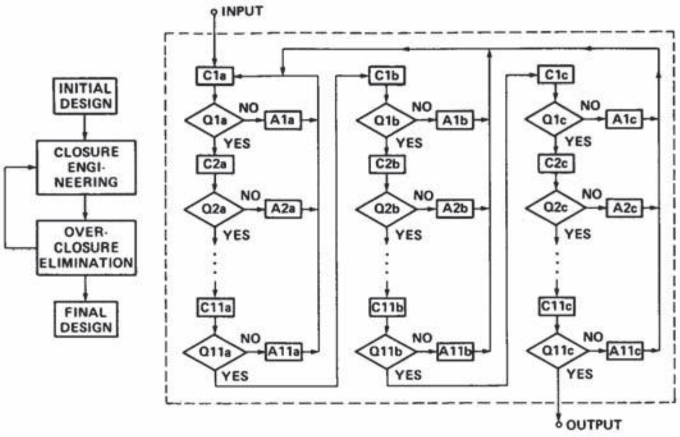
According to the NASA study final report:[2] "In actual practice, the achievement of full closure will be a highly complicated, iterative engineering design process.*** Every factory system, subsystem, component structure, and input requirement must be carefully matched against known factory output capabilities. Any gaps in the manufacturing flow must be filled by the introduction of additional machines, whose own construction and operation may create new gaps requiring the introduction of still more machines. The team developed a simple iterative procedure for generating designs for engineering systems which display complete closure. The procedure must be cumulatively iterated, first to achieve closure starting from

---

** Ford's River Rouge complex,[2684] built beginning in 1918 on an 1,100-acre site outside Detroit, achieved nearly 100% parts fabrication and assembly closure in the manufacture of automobiles nearly a century ago. Henry Ford's ships delivered iron ore, lumber and limestone from his mines, mills and quarries in Michigan's Upper Peninsula. Coal was barged in from his fields in West Virginia and Kentucky for energy. Rubber came straight from his plantations in Brazil. These raw materials entered one end of the factory and moved around on the Rouge's 100-mile internal railroad, allowing Ford Motor to manufacture its own iron, steel, glass, tires and engines. Finished cars, tractors, and even Navy submarine chaser ships emerged from the other end of the plant.*

*** Some have asserted that the mere existence of a large manufacturing economy is not by itself a good proof of the possibility of closure because such an economy includes humans, and without depending on human self-reproduction such a system could soon cease to exist.[1850] This argument is incorrect for at least two reasons. First, if a successful nanotechnology-based medicine succeeds in eliminating biological aging,[2685] a manufacturing economy populated exclusively by nonreproducing humans could persist indefinitely. Second, a manufacturing economy that produces all of its own structure is properly termed self-replicating, regardless of whether its source of control is teleoperation (by humans) or full autonomy (Section 5.1.9 (A1)).*

**** To get a sense of the complex iterative nature of closure engineering, the reader should ponder the design process that he or she might undertake in order to generate the following full-closure self-referential "pangram"[2687] (a sentence using all 26 letters at least once), written by Lee Sallows and reported provided by Hofstadter:[260] "Only the fool would take trouble to verify that his sentence was composed of ten a's, three b's, four c's, four d's, forty-six e's, sixteen f's, four g's, thirteen h's, fifteen i's, two k's, nine l's, four m's, twenty-five n's, twenty-four o's, five p's, sixteen r's, forty-one s's, thirty-seven t's, ten u's, eight v's, four x's, eleven y's, twenty-seven commas, twenty-three apostrophes, seven hyphens, and, last but not least, a single !" Self-enumerating sentences like these are also called "Sallowsgrams"[2687] and have been generated in English, French, Dutch, and Japanese languages using iterative computer programs.*



EXPLANATION OF SYMBOLS

PROCEDURAL QUERIES = Q

Q1a – CAN SYSTEM ASSEMBLE ALL MACHINES OF WHICH IT IS COMPRISED?
Q2a – CAN SYSTEM ASSEMBLE ALL SUBASSEMBLIES OF WHICH ITS MACHINES ARE COMPRISED?
Q3a – CAN SYSTEM MACHINE ALL PARTS OF WHICH ITS MACHINES ARE COMPRISED?
Q4a – CAN SYSTEM EXTRACT ALL MATERIALS OF WHICH ITS PARTS ARE COMPRISED?
Q5a – CAN SYSTEM MINE ALL MINERALS OF WHICH ITS MATERIALS ARE COMPRISED?
Q6a – CAN SYSTEM TRANSPORT ALL (MACHINES/SUBASSEMBLIES/PARTS/MATERIALS/MINERALS) OF WHICH IT IS COMPRISED?
Q7a – CAN SYSTEM VERIFY ALL (MACHINES/SUBASSEMBLIES/PARTS/MATERIALS/MINERALS) OF WHICH IT IS COMPRISED?
Q8a – CAN SYSTEM WAREHOUSE ALL (MACHINES/SUBASSEMBLIES/PARTS/MATERIALS/MINERALS) OF WHICH IT IS COMPRISED?
Q9a – CAN SYSTEM REPAIR ALL SUBSYSTEMS OF WHICH IT IS COMPRISED?
Q10a – CAN SYSTEM COMPUTERS CONTROL ALL SUBSYSTEMS OF WHICH IT IS COMPRISED?
Q11a – CAN SYSTEM ENERGY PLANT ENERGIZE ALL SUBSYSTEMS OF WHICH IT (THE SYSTEM) IS COMPRISED?

Q1b – CAN SYSTEM ASSEMBLE ENOUGH MACHINES TO REPLICATE THE ORIGINAL SYSTEM?
Q2b – CAN SYSTEM ASSEMBLE ENOUGH SUBASSEMBLIES TO REPLICATE THE ORIGINAL SYSTEM?
⋮
Q11b – CAN SYSTEM ENERGY PLANT PRODUCE ENOUGH ENERGY TO PERMIT REPLICATION OF THE ORIGINAL SYSTEM?

Q1c – CAN SYSTEM ASSEMBLE MACHINES FAST ENOUGH TO REPLICATE THE ORIGINAL SYSTEM WITHIN ESTABLISHED TIME CONSTRAINTS?
⋮
Q11c – CAN SYSTEM ENERGY PLANT PRODUCE ENOUGH ENERGY FAST ENOUGH (HIGH ENOUGH *POWER*) TO REPLICATE THE ORIGINAL SYSTEM WITHIN ESTABLISHED TIME CONSTRAINTS?

SYSTEM COMPONENTS LISTS = C

C1a, b, c – MACHINES
C2a, b, c – SUBASSEMBLIES
C3a, b, c – PARTS
C4a, b, c – MATERIALS
C5a, b, c – MINERALS (SUBSTRATE)
C6a, b, c – TRANSPORTATION FACILITIES
C7a, b, c – VERIFICATION FACILITIES
C8a, b, c – STORAGE FACILITIES
C9a, b, c – REPAIR FACILITIES
C10a, b, c – COMPUTER FACILITIES
C 11a, b, c – ENERGY FACILITIES

SYSTEM COMPONENTS ACTION LIST = A

A1a, b, c – NEW MACHINES
A2a, b, c – NEW SUBASSEMBLY-MAKING MACHINES
⋮
A11a, b, c – NEW ENERGY FACILITY-MAKING MACHINES
A#a – Add new machines to make . . .
A#b – Add new machines to make . . .
A#c – increase replication time available or change machine design for . . .

Figure 5.7. Generalized closure engineering design cycles. (from 1980 NASA study,[2] at Section 5.3.6 and Figure 5.22)

some initial design, then again to eliminate overclosure to obtain an optimized design. Each cycle is broken down into a succession of subiterations which ensure qualitative, quantitative, and throughput closure. In addition, each subiteration is further decomposed into design cycles for each factory subsystem or component." A few subsequent attempts to apply closure analysis have concentrated largely on qualitative materials closure in machine replicator systems while de-emphasizing quantitative and nonmaterials closure issues,[1128] or have considered closure issues only in the more limited context of autocatalytic chemical networks.[2367,2686] However, Suh[1160] has presented a systematic approach to manufacturing system design wherein a hierarchy of functional requirements and design parameters can be evaluated, yielding a "functionality matrix" (Figure 3.61) that can be used to compare structures, components, or features of a design with the functions they perform, with a view to achieving closure.

Partial closure results in a system that is only partially self-replicating. With partial closure, the machine system will fail to self-replicate if some vital matter, energy, or information input is not provided from the outside. For instance, various preliminary studies[2688-2690] of the materials closure problem in connection with the possibility of macroscale "bootstrapping" in space manufacturing have concluded that 90-96% closure is attainable in specific nonreplicating manufacturing applications. The 4-10% that still must be supplied are sometimes called "vitamin parts." (The classic example of self-replication without complete materials closure: Humans self-reproduce but must but take in vitamin C, whereas most other self-reproducing vertebrates can make their own vitamin C).[2691] In the case of macroscale replicators, vitamin parts might include hard-to-manufacture but lightweight items such as microelectronics components, ball bearings, precision instruments, and other parts which might not be cost-effective to produce via automation off-Earth except in the longer term. To take another example, partial information closure might imply that factory control or supervision is provided from the outside, perhaps (in the case of a lunar facility) from Earth-based computers programmed with human-supervised expert systems or from manned remote teleoperation control stations located on Earth or in low Earth orbit.

Regarding closure engineering, Friedman[573] observes that "if 96% closure can really be attained for the lunar solar cell example, it would represent a factor of 25 less material that must be expensively transported to the moon. However, ...a key factor ... which deserves more emphasis [is] the ratio of the weight of a producing assembly to the product assembly. For example, the many tons of microchip manufacturing equipment required to produce a few ounces of microchips makes this choice a poor one — at least early in the evolution — for self-replication, thus making microelectronics the top of everyone's list of 'vitamin parts'."

This conclusion makes sense for macroscale replicators but not for microscale replicators or nanofactory-based molecular manufacturing systems. The replicator/product mass ratio for a several-ton microchip fabrication machine (itself containing a few ounces of microchips) may be ~35,000 (i.e., several tons / several ounces). However, the Drexler manipulator arm (Section 4.9, Figure 4.29) that might be used for positional-assembly style molecular manufacturing is composed of ~4 million atoms and has only ~50 parts (averaging 82,000 atoms/part), so a manipulator arm producing its own parts has a replicator/product mass ratio of only ~50. Furthermore, if the microchip fabrication machine has a mean product cycle time of ~1 minute per chip (taking into account the multiple chips on each wafer), then the machine requires ~2 x 10^6 sec (24 days) to fabricate its own mass of microchips. By contrast, the Drexler manipulator arm is designed for a 1 MHz atom placement rate, hence would fabricate its own mass of nanomachinery in ~4 sec, a 6 orders-of-magnitude improvement.

It has been pointed out[1054] that if a system is "truly isolated in the thermodynamic sense and also perhaps in a more absolute sense (no exchange of information with the environment) then it cannot be self-replicating without violating the laws of thermodynamics." While this may be true for systems with no onboard stores of raw materials, energy, and information, it should also be noted that a replicating system which achieves 100% closure is not "closed" or "isolated" in the classic thermodynamic sense. Materials, energy and information continue to flow into the system — it is thermodynamically "open" — but these flows are of local origin and could be managed autonomously by the replicator itself without need for direct human intervention or external supplementation.

Our use of the term "closure" should also be carefully distinguished from: (1) the "closure index" described by Russell and Kime[2692] in connection with computer fault diagnosis and "system closure" as used in fault-tolerant computing,[2693,2694] (2) the widespread use of the terms "form closure" and "force closure" in relation to visual recognition[2695] and parts grippers[2696] used in robotics manufacturing technology, (3) Pattee's principle of self-organization known as semantic closure which allows open-ended evolution,[2381-2385] and (4) other completely unrelated uses of "closure" in apparel manufacturing,[2697] clinical psychology,[2698] education,[2699] linguistics,[2700] literature,[2701,2702] trauma surgery,[2703] and various other disciplines.[2369-2371]

5.7 Massively Parallel Molecular Manufacturing

Complex objects assembled from simpler components may be manufactured either serially or in parallel. In serial assembly, objects are manufactured one at a time by a stepwise manufacturing process. Examples include handcrafted unique items such as an antique pocket watch, classical industrial "mass production" items such as automobiles which emerge only one by one at the end of a linear assembly line, or the traditional serial digital computer which executes instructions one by one in a linear sequence. In parallel assembly, objects are manufactured along many pathways simultaneously or at many different sites, such as polysomes in living cells (multiple ribosomes translating a single mRNA strand simultaneously), mask lithography deposition of multiple circuits simultaneously on a single semiconductor wafer, or the modern parallel computer which at any moment is executing different instructions on thousands or even tens of thousands of independent processors in a highly parallel manner. Parallel manufacturing systems could have many possible control/configuration architectures, analogous to: a SIMD (Single Instruction Multiple Data) approach;[2704] convergent (Section 5.9.4) or fractal[2705-2707] assembly; agoric algorithms;[780-783] stigmergy,[2708,2709] swarm,[912,2710] amorphous computing,[2711,2712] or agent-based[783,811-814] approaches; kinematic cellular automaton assembly lines;[815] or other manufacturing analogs taken from high-performance parallel computing[815] such as SMP (Symmetric MultiProcessors),[2713-2716] MPP (Massively Parallel Processors),[2717] and NOWs/COWs (Networks/Clusters of Workstations).[2714,2718]

Biology provides perhaps the best example of the power of massive parallelism in assembly. A single ribosome (Section 4.2), able to make a single protein as directed by a single molecule of messenger RNA, is a marvelous manufacturing system. Yet by itself, it would have little economic impact. But multiple millions of ribosomes, operating together in each living cell, can make all the proteins in a tree or — still more quickly — all the proteins in a rapidly growing kelp plant[2719] which can grow up to six inches per day.

The difference between serial and parallel processing is equally crucial in molecular manufacturing where the basic parts are very small. If a typical molecularly precise simple component is 1 nm^3 in volume, then to manufacture a single macroscale but molecularly precise 1 cm^3 product requires the assembly of 1000 billion billion (10^{21}) individual simple molecular components. With serial manufacturing, just one molecular component is handled at a time — even at a 1 GHz operating frequency it would take many thousands of years, clearly not economically viable. But with parallel manufacturing, vast numbers of molecular components can be processed simultaneously, reducing batch processing times to days, hours, or even less. **Massively parallel assembly is the key to the economic viability of molecular manufacturing**.

There are two principal pathways for achieving massively parallel assembly of molecularly precise physical structures: self-assembly and positional assembly. In commercial chemical synthesis, self-assembly usually takes place in fluid phase among mole (~10^{23}) quantities of reactant molecules, which interact to produce mole quantities of product molecules. In Seeman's experiments[1448] producing DNA-based structures and in other related experiments involving supramolecular or biomolecular self-assembly (Section 4.1), the yield of product objects per batch may be vastly less than mole quantities but is still quite large by conventional standards in macroscale manufacturing. The inherent parallelism of self-assembly is the main advantage of this pathway over positional assembly in manufacturing.

In order to overcome this advantage and reap the full benefits of flexibility, precision and quality in 21st century molecular manufacturing using positional assembly — also known (in the context of molecular manufacturing) as machine-phase nanotechnology — new techniques for massively parallel positional assembly must be developed. At least two such techniques have already been clearly identified: (1) massively parallel manipulator arrays and (2) self-replicating manipulator systems.

1. **Massively parallel manipulator arrays** would use a very large array of independently actuated manipulation devices (e.g., scanning probe tips, robot arms, etc.) to process a very large number of molecularly precise components simultaneously to build a larger product object. In order to produce large numbers of nanoparts and nano-assemblies, massively parallel scanning probe microscope (SPM) arrays[2720,2721] and microscale SPMs[2722-2725] would be most convenient. Force-sensing devices such as piezoelectric,[2726] piezoresistive,[2727] and capacitive[2728] microcantilevers made it possible to construct microscale atomic force microscopes (AFMs) on chips without an external deflection sensor. (We exclude fixed-tip arrays[2729,2730] in the following discussion.) In 1995, Itoh and colleagues[2731] at the University of Tokyo fabricated an experimental piezoelectric ZnO_2-on-SiO_2 microcantilever array of ten tips on a single silicon chip. Each cantilever tip lay ~70 microns from its neighbor, and measured 150 microns long, 50 microns wide and 3.5 microns thick, or ~26,000 $micron^3$/device, and each of the devices could be operated independently in the z-axis (e.g., vertically) up to near their mechanical resonance frequencies of 145-147 KHz at an actuation sensitivity of ~20 nm/volt — for instance, 0.3-nm resolution at 125 KHz.

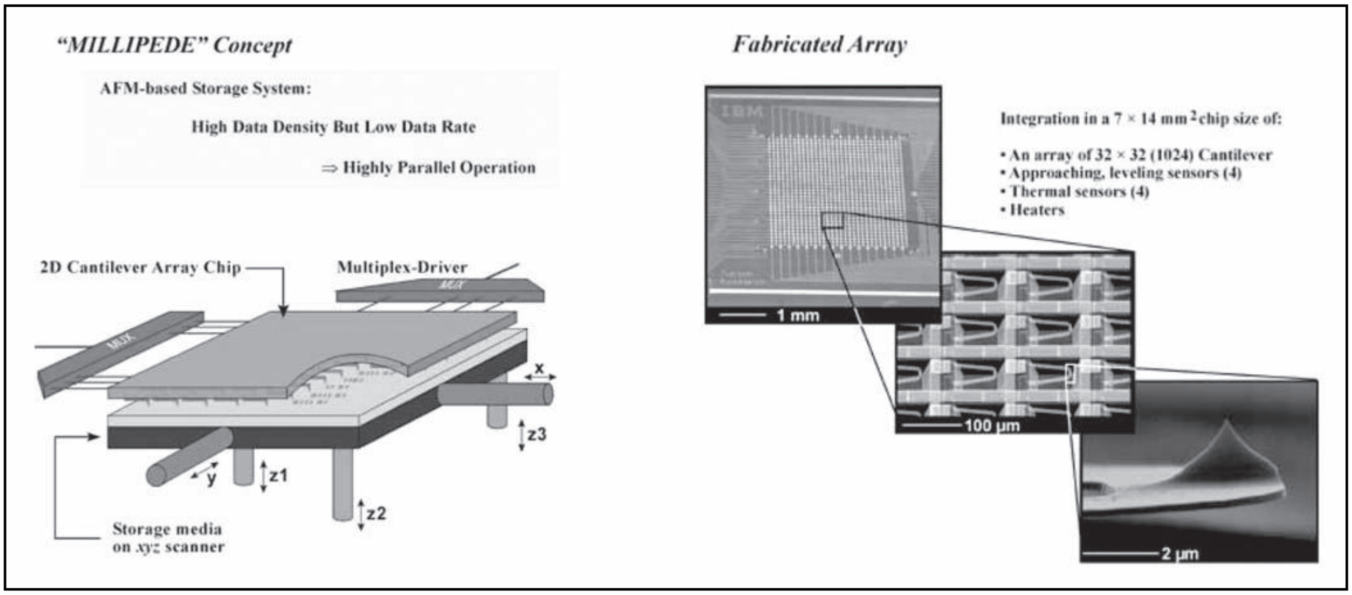

"MILLIPEDE" Concept
AFM-based Storage System:
High Data Density But Low Data Rate
⇒ Highly Parallel Operation
2D Cantilever Array Chip
Multiplex-Driver
MUX
MUX
x
y
z1
z2
z3
Storage media on xyz scanner
Fabricated Array
IBM
Integration in a 7 × 14 mm^2 chip size of:
• An array of 32 × 32 (1024) Cantilever
• Approaching, leveling sensors (4)
• Thermal sensors (4)
• Heaters
1 mm
100 µm
2 µm

Figure 5.8. Millipede concept of IBM Zurich Research Laboratory — schematic of cantilever tip array on a chip positioned over a flat surface indented with data-carrying Braille-like pits, shown at left; actual images of a fabricated array shown at right. (courtesy of IBM[2755,2756])

Parallel probe scanning and lithography has been achieved by Quate's group at Stanford, which has progressed from simple piezoresistive microcantilever arrays with 5 tips spaced 100 microns apart and 0.04-nm resolution at 1 KHz but only one z-axis actuator for the whole array,[2732] to arrays with integrated sensors and actuators that allow parallel imaging and lithography with feedback and independent control of each of up to 16 tips, with scanning speeds up to 3 mm/sec using a piezoresistive sensor.[2733,2734] By 1998, Quate's group had demonstrated[2735-2742] arrays of 50-100 independently controllable AFM probe tips mounted in 2-D patterns with 60 KHz resonances, including a 10 x 10 cantilevered tip array fabricated in closely spaced rows using throughwafer interconnects on a single chip, and this work continues.[2743-2745]

MacDonald's group at the Cornell Nanofabrication Facility pursued similar goals. In 1991, the team fabricated their first submicron stylus, driven in the xy plane using interdigitating MEMS comb drives,[2746] including the first opposable tip pair. By 1993, they had produced a 25-tip array on one xyz actuator,[2747,2748] and by 1995 a complete working micro-STM (including xy comb drives) measuring 200 microns on an edge and a micro-AFM measuring 2 mm on an edge including a 1-mm long cantilever with a 20-nm diameter integrated tip on a 6-micron high by 1-micron diameter support shaft.[2749,2750] MacDonald's group then demonstrated tip arrays with 5 micron spacings, exploiting the same process used to make the working micro-STM.[2751,2752] With the same technology tips or small arrays of tips could be spaced 25-50 microns apart and integrated with individual z-axis microactuators, so that one xy-axis manipulator could support many tips with each tip having a separate z actuator. By 1997, the group[2753] had built and tested an array of micro-STMs on the surface of an ordinary silicon chip, with each tip on a cantilever 150 microns long with 3-D sensing and control. The largest prototype array had 144 probes,[2754] arranged in a square consisting of 12 rows of 12 probes each, with individual probe needles about 200 microns apart. Further development was to focus on increasing the range of movement and on fitting more and smaller probes into the same space.

Using conventional microlithography, researchers in the Millipede project at IBM's Zurich Research Laboratory[2755,2756] have fabricated scanning probe tip arrays of up to 1024 individual tips (Figure 5.8) to achieve terabit-per-square-inch data storage densities.[2757,2758] Simpler mechanical ciliary arrays consisting of 10,000 independent microactuators on a 1 cm^2 chip have been fabricated at the Cornell National Nanofabrication Laboratory for microscale parts transport applications,[2759,2760] and other ciliary array systems for parts presentation in microscale manufacturing have been reported by many others including the Fujita group,[2761-2766] Bohringer and colleagues,[2767-2777] Will's group,[2778-2784] Darling, Suh and Kovacs,[2785-2787] and others.[2788-2793] Microcantilever arrays for "electronic nose"[2794-2803] and other applications[2006-2009] have also been constructed, in at least one case having millions of interdigitated cantilevers on a single chip.[2804] A probe-array-based "micro-factory" for site-specific deposition of desired molecular feedstock moieties from gas phase onto a planar workpiece surface has been proposed.[2805]

Active probe arrays for dip-pen nanolithography using DNA-based "ink" have been developed by Mirkin's group.[2806-2813] At a Materials Research Society meeting in late 2002,[2026] Mirkin reported that his group had constructed an array of 10,000 microscope tips, each capable of acting independently from the others. By using 10 tips in concert they can draw essentially any desired shape. "The goal is to use dip pen nanolithography to generate [DNA-based] templates on surfaces that guide the assembly of nanoscale building blocks," Mirkin says. "It opens the door to placing electronic particles right where you want them. We think it's ultimately going to be a production tool....This is not going to stop at 10,000. We can make arrays of arrays." Proteins can be laid down in similar manner.[1255] Another approach is the use of independently mobile multiple manipulator platforms such as the NanoWalker system under investigation by Martel's group.[2814-2817] Martel envisions a fleet[2818] of such wireless instrumented microrobots collectively forming a nanofactory system that could be used for positional nanomanufacturing operations.

Yet another alternative is Zyvex's Rotapod™ exponential assembly design concept (Section 4.17),[576] in which a single robotic arm on a wafer (Figure 4.52) makes a second robotic arm on a facing surface by picking up micron-size lithographically-produced parts — carefully laid out in advance in exactly the right locations so the tiny robotic arm can find them — and assembling them (Figure 4.53). The two robotic arms then make two more robotic arms, one on each of the two facing surfaces. These four robotic arms, two on each surface, then make four more robotic arms. This process continues with the number of robotic arms steadily increasing in the pattern 1, 2, 4, 8, 16, 32, 64, etc., until some manufacturing limit is reached (e.g., both surfaces are completely covered with tiny robotic arms). Thus a single manipulator uses supplied parts to build a large manipulator array (Figure 4.54) which can subsequently undertake the desired massively parallel manufacturing operations. However, the present Rotapod™ manipulator design is still under development as it requires more precision to achieve flexible and molecularly precise fabrication. In 2001, Zyvex was awarded a $25 million, five-year, National Institute of Standards and Technology Advanced Technology Program (NIST-ATP) government contract to develop prototype microscale assemblers using microelectromechanical systems (MEMS) and nanoelectromechanical systems (NEMS) for prototype nanoscale assemblers.[2247]

2. **Self-replicating manipulator systems** achieve massively parallel assembly first by fabricating copies of themselves, then allowing those copies to fabricate further copies, resulting in a rapid increase in the total number of systems. Once the population of replicated manipulator systems is deemed large enough (Section 5.9.6), the manipulator population is redirected to produce useful product objects rather than more copies of itself. Self-replicating systems are widely found in natural biological systems but have not been pursued explicitly in macroscale manufacturing for at least two reasons: (1) the widespread but erroneous perception of great technical difficulty, and (2) the correct perception that such massive parallelism is unnecessary for traditional macroscale manufacturing. Nevertheless, ever since John von Neumann's theoretical studies of replicating systems in the 1940s and 1950s, and the well-known 1980 NASA engineering study of self-replicating lunar factories (Section 3.13), manufacturing automation has been slowly progressing toward the goal of the fully self-replicating factory — including most notably Fujitsu Fanuc's nearly "unmanned" robot factory in Yamanashi Prefecture that uses robot arms to make robot arms (Figures 3.13 and 3.14). It's worth recalling that self-replicating systems can be fully remote-controlled, fully autonomous, or any combination in between.

Both parallel manipulator arrays and individual replicators can be "self-replicating." The parallel arrays can build additional parallel arrays, after which the collective population of array manipulators builds useful products. Similarly, the individual replicators can build additional individual replicators, then the collective population of replicators builds useful products. Each approach offers certain advantages and disadvantages — array systems can be more efficient due to positional specialization of workflow processing, while individual replicators are more tolerant of single-component failures — but both approaches exemplify "self-replication."

In the last few years there has been renewed research interest in the challenge of mechanical self-replicating systems, in part due to the realization that replication can be a fundamentally simple process. For example, Joseph Jacobson at the MIT Media Lab suggests[1930] that "to be useful for many applications, engineered systems must be able to manufacture multiple copies. Self-replicating systems may be useful in attaining that goal and it represents a new discipline in engineering." Today there are several ongoing university research programs, both theoretical and experimental, on mechanical (nonbiological) self-replicating machines, as described elsewhere in this book. The biotechnology and molecular engineering communities are just beginning to seriously study mechanical replicators operating in the nanoscale size domain (Sections 4.4 and 4.5). Current methods of self-assembly, while allowing massively parallel assembly, lack the flexibility, precision and quality that are needed for 21st century molecular manufacturing. Current methods of positional assembly, including massively parallel manipulator arrays and self-replicating manipulator systems, should allow molecularly precise massively parallel assembly, although further theoretical and experimental work will be required to fully realize this capability.

5.8 Software Simulators for Robots and Automated Manufacturing

Valentí Pineda,[1314] an industrial robotics and automation engineer, notes that in common practice the use of accurate software simulators can save a lot of time, money and effort in a project, and also "are sometimes a powerful argument to convince a customer to make an investment when they see a virtual factory performing virtual work with their name written somewhere in the working cell."

Some of the benefits of simulators in industrial robotics may be applicable to robotic/automated replicators, including: (1) calculation of the optimum layout that favors industrial processes needed for the fabrication of the replicated unit; (2) calculation and verification of job concept before undertaking the real work, allowing a determination of which operations are possible and which ones are not; (3) optimizing the design of devices, pieces and sub-assemblies for most effective grasping, recognition and reaching the position effectively by robots; (4) deciding how many robots and devices are required to successfully complete the operations; (5) optimization of required resources prior to the hardware implementation; and (6) operational testing of all the above to verify and overcome positioning problems.[1314]

Besides robotics simulators, many other types of software may help in the design and testing of replicators. For example, 3-D drawing software (e.g., SolidWorks, AutoCAD (AutoDesk), 3D Studio Max, etc.) allows the engineer to see what the best assembly process should be and to simulate pieces in motion. The 3-D files can be exported back to robotic simulation software (e.g., CimStation Robotics,[2819] Deneb/IGRIP (Interactive Graphics Robot Instruction Program),[2820] MotoSim,[2821] WorkSpace,[2822] and mobile robotics simulators[2823]), using which various aspects of robotic manufacturing operations can be tested — including kinematics, dynamics, motion planning, verification of production concepts, workcell designs, and manufacturing processes — prior to physical implementation. Design for Assembly software tools facilitate development of multilevel assemblies, sequences, part paths and process documentation.[2824] Other types of software permit testing of wear, thermal stress, mechanical stress, and so forth. The use of visual programming languages (e.g., Visual Basic or Visual C++) also permits the simulation of chemical or physical processes implementing equations in the program and showing a visual output of the processes, such as the simulation of an expert system controlling a chemical reactor.[1314] General purpose manufacturing process simulation packages such as Flexsim,[2825] ShowFlow[2826] and SimCAD[2827] are well known.

At the high end of complex machine design, we have, for example, the comprehensive 3-D modeling tools of Dassault Systems, which Boeing used in the early 1990s to create the world's first entirely digitally designed aircraft (thus avoiding the expense of creating physical prototypes). Subsequent generations of this software are now being used to implement "product lifecycle management," suggesting a coordinated process by which thousands of engineers located around the world might, in the future, cooperate in the design of a single complex nanorobotic system containing millions of parts and billions of atoms. Explains one writer,[2996] of the Boeing effort: "If the supplier of a section of the fuselage, say, decides to move the location of a door by 2 inches, that will affect the design of everything around it, from the placement of windows to the location of hidden wiring bundles. In the past such a change in the door would require weeks to redesign adjoining parts. Dassault's software instead will allow designers anywhere to instantly know how a modification in their piece of the [aircraft] will affect every other part of the plane. The software will also allow Boeing to simulate the way the plane will be assembled in the factory before a single piece of machinery is purchased, [avoiding] costly delays if engineers need to rejigger factory bottlenecks. The software can also simulate wear and tear over many years to predict, for instance, when a hydraulic pump is likely to fail."

5.9 Brief Mathematical Primer on Self-Replicating Systems

Given the vastness of the replicator design space (Section 5.1.9), it is impossible in the limited space available here to attempt even a balanced summary of the mathematics of self-replication that might apply to each class of replicator. Each of the 137 design dimensions described in Section 5.1.9 requires a painstaking mathematical analysis whose full specification lies considerably beyond the scope of this book. We will describe here only a few of the most basic concepts, including Fibonacci numbers (Section 5.9.1), exponential population growth strategies (Section 5.9.2) and limitations (Section 5.9.3), and finally the general performance of convergent assembly manufacturing systems (Section 5.9.4), power law scaling (Section 5.9.5), and design tradeoffs related to nanofactory process specialization (Section 5.9.6).

5.9.1 Fibonacci's Rabbits

Leonardo Fibonacci (1175-1250) was the greatest European mathematician of the Middle Ages. His full name was Leonardo of Pisa, or Leonardo Pisano in Italian since he was born in Pisa, the city with the famous Leaning Tower.[2828] In his first book,[2829] originally published in 1202, Fibonacci introduces the following problem:

A pair of rabbits are put in a field and, if rabbits take a month to become mature and then produce a new pair every month after that, how many pairs will there be in twelve months time?

In his solution to this puzzle, Fibonacci assumes that no rabbits ever escape and none die, and no extra rabbits are introduced into the field except those born from this original pair. He puts a newborn pair of rabbits, one male, one female, in a field and allows the rabbits to mate at the age of one month so that at the end of its second month a female can produce another pair of rabbits. He further assumes that the female **always** produces one new pair (one male, one female) **every month** from the second month on. The course of rabbit reproduction, illustrated in Figure 5.9, proceeds as follows:[2828]

Start of Month 1: The rabbits are placed in the field but have not mated; there is only 1 pair.
End of Month 1: The rabbits mate; there is only 1 pair in the field.
End of Month 2: The female produces one new pair; there are now 2 pairs in the field.
End of Month 3: The original female produces a second pair; there are now 3 pairs in the field.
End of Month 4: The original female has produced yet another new pair, the female born two months ago produces her first pair also; there are now 5 pairs in the field.
End of Month 5: ...and so on, adding the latest two numbers to get the next one.

The total number of pairs of rabbits in the field at the start of each month, counting from month n = 1, is: 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, and there are 233 pairs at the end of month 12. The French mathematician Edouard Lucas (1842-1891)[2830-2832] first gave the name "Fibonacci numbers" to this series. The Fibonacci sequence appears extensively in nature,[2833,2834] especially in botany.

To express this progression mathematically as a recurrence relation,[2835] we define F(n) as the number of pairs of rabbits in the field at the *start* of month n. Then F(0) = 0, F(1) = 1, and:

$$F(n) = F(n-1) + F(n-2) \qquad \text{(Eqn. 1)}$$

for n > 1. The number of pairs at the *end* of month n is simply:

$$F_{end}(n) = F(n+1) \qquad \text{(Eqn. 2)}$$

and the total elapsed time is $t = n\tau$, where τ is the replication (or gestation) time, the units of time required for each replication cycle to be completed. τ = 1 month in this example.

Interestingly, the ratio of successive Fibonacci numbers, $F(n-1) / F(n-2)$, approaches a constant value ϕ as $n \rightarrow \infty$. The constant ϕ (phi) is often called the golden mean (Euclid[2836]), the golden section (Leonardo da Vinci), the golden ratio, or the golden number (see value, below). ϕ is given explicitly by the relation:

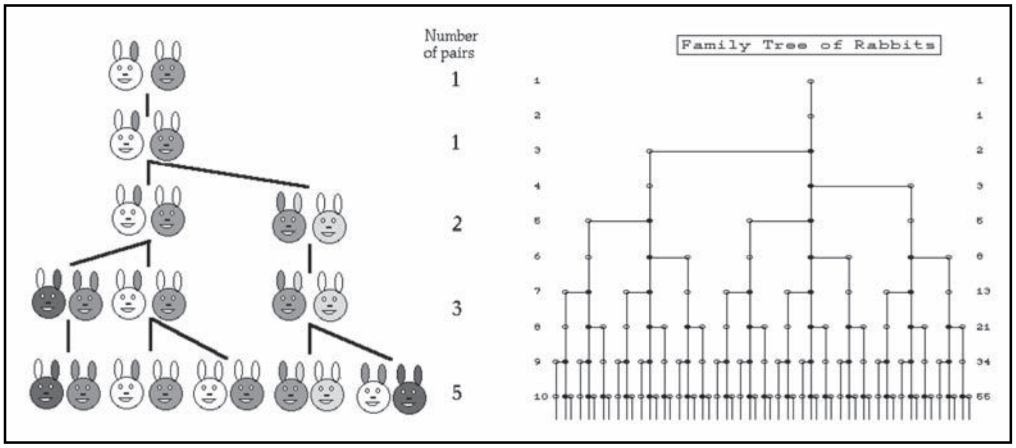


Figure 5.9. Successive generations of Fibonacci's rabbits. (courtesy of Ron Knott[2828])

$$\phi = (1 + 5^{1/2}) / 2 \qquad \text{(Eqn. 3)}$$

and according to Binet's formula for the nth Fibonacci number (apparently actually devised first by the mathematician A. de Moivre in 1730, more than a century before J.P.M. Binet rediscovered it in 1843),[2837] the nth value of the Fibonacci series is given exactly by:

$$F(n) = (\phi^n - (-\phi)^{-n}) / 5^{1/2} \qquad \text{(Eqn. 4)}$$

for all positive integers n, where ϕ = 1.61803 39887 49894 84820 45868 34365 63811 77203 09179 80576 .... Knott[2838] points out that since $\text{abs}(-(-\phi)^{-n}) < 1$ for $n > 0$, the influence of this term decreases rapidly with increasing n, allowing the exact formula to be simplified further to:

$$F(n) = \text{round}(\phi^n / 5^{1/2}) \qquad \text{(Eqn. 5)}$$

where the "round" function gives the nearest integer to its argument.

The rabbit formula (Eqn. 4) assumes that newborn rabbits are "birth-immature replicators" — they require some length of time (one cycle in this example) to mature before they can begin reproducing at the rate of one offspring per cycle. Taneja and Walsh[1073] have generalized the rabbit formula to allow for a variable maturation time τ_{mat}, where τ_{mat}/τ = 1, 2, 3, 4, ..., showing that the number of pairs at the end of n cycles is:

$$F_{mat}(n, \tau_{mat}/\tau) = M(1) + M(2) + \ldots + M(n) \qquad \text{(Eqn. 6)}$$
$$1 \le n \le (\tau_{mat}/\tau + 1)$$

$$F_{mat}(n, \tau_{mat}/\tau) = 2M(n-1) + M(n-2) + \ldots + M(n - 1 - \tau_{mat}/\tau)$$
$$n \ge (\tau_{mat}/\tau + 2) \qquad \text{(Eqn. 7)}$$

$$M(1) = M(2) = \ldots = M(\tau_{mat}/\tau + 1) = 1 \qquad \text{(Eqn. 8)}$$

$$M(n) = M(n-1) + M(n - 1 - \tau_{mat}/\tau) \qquad \text{(Eqn. 9)}$$
$$n \ge (\tau_{mat}/\tau + 2)$$

where M(n) is the number of adult replicators (capable of replication) in the nth cycle. Birth-immature replicators that require more than one cycle to reach maturity may be called "extended-maturation replicators." Note that human beings are very extended maturation replicators, with $\tau_{mat}/\tau \sim 17.0$ currently in the United States, assuming a replicator gestation time of τ = 0.736 year (~9 months) and a replicator maturation time of τ_{mat} = 12.54 years, the average age of menarche (first menstruation) for U.S. females during 1988-1994[2839] (cf. 12.75 years during 1963-1970 in U.S.,[2839] 12.9 years in U.K.,[2840] and from 12-18 years across various cultures and throughout history[2841]).

Phares and Simmons[2842] have derived a sum rule for the generalized form of the Eqn. 1 recurrence relation $F(n) = a \cdot F(n-1) + b \cdot F(n-2)$, where a and b are arbitrary constant coefficients that could perhaps be used to represent post-pregnancy alterations in replicator fecundity.

5.9.2 Strategies for Exponential Kinematic Self-Replication

Fibonacci's rabbits must wait one time period to mature before they can begin replicating, markedly slowing the population growth rate. But consider a replicator that is a fully functional adult device from birth and can immediately begin the construction of its own daughter without waiting. Such entities may be called "birth-mature replicators." At the end of the first cycle (n = 1), there are 2 adult devices, the first having constructed the second. At the end of the second cycle (n = 2), there are 4 adult devices, each of the first-cycle devices having constructed their own copies. The series progression, starting from the end of the first replication cycle, is therefore 2, 4, 8, 16, ..., and so the population of birth-mature replicators follows the simple exponential law:

$$P(n) = 2^n \qquad \text{(Eqn. 10A)}$$

$$P(t) = 2^{t/\tau} \qquad \text{(Eqn. 10B)}$$

after n cycles have elapsed; $P(n) > F_{end}(n)$ for all $n > 0$. Note that the replicator population can be restated as P(t) in terms of t, the total elapsed time since replication began, and the replication time τ, the time a replicator requires to complete a replication cycle.

Even faster population growth $P_{fast}(n) > P(n)$ may be obtained by placing each completed subunit of the daughter that is currently being built into full productive use immediately, instead of waiting for the final completion of the daughter device. There are many design configurations where something close to this can be achieved efficiently, most notably the factory models (e.g., Sections 3.11, 3.13.2.2, 3.15, 4.9.3, 4.14, and 5.9.6) wherein more specialized subunits within the factory (e.g., an individual lathe) could be pressed into immediate service prior to completion of the entire factory (Freitas and Gilbreath,[2] Section 5.3.5 at p. 218; see also "Operating-Subsystem-in-Process Replication", Section 5.1.8), and there has been at least one experimental demonstration of this by the Chirikjian group (see "Robot 4" in Section 3.23.2 and Figure 3.75).

Let us consider that the replication cycle is divided into k time segments, such that at the end of each time segment all components built during that time segment can begin fully contributing to replicative activities. For k = 1, the base population of fast replicators $p_{fast}(1) = 1 + 1$ (replicator plus daughter) = 2 devices, at the end of the n = 1 cycle. For k = 2, at the end of half a cycle, the original replicator has built half a daughter, and that half now enters service. By the end of the replication cycle, the second half of the daughter has been built by the original replicator and the daughter has also had half a cycle to begin construction of a granddaughter device, which is now one-quarter completed; hence $p_{fast}(1) = 1 + 2 \cdot (1/k) + 1 \cdot (1/k)^2 = 2.25$ devices. For k = 3, $p_{fast}(1) = 1 + 3 \cdot (1/k) + 3 \cdot (1/k)^2 + 1 \cdot (1/k)^3 = 2.37$ devices; for k = 4, $p_{fast}(1) = 1 + 4 \cdot (1/k) + 6 \cdot (1/k)^2 + 4 \cdot (1/k)^3 + 1 \cdot (1/k)^4 = 2.44$ devices produced during the n = 1 replication cycle. Since the coefficients of each term are horizontal elements of Pascal's triangle,* which is a two-dimensional number array constructed by sequential addition much like Fibonacci numbers, it can be shown that $p_{fast}(n) = p_{fast}(n, 1) + p_{fast}(n, 2) + \ldots$ is an infinite series with the individual terms:

$$p_{fast}(n, 1) = 1 \text{ (constant)}$$

$$p_{fast}(n, 2) = [k] \cdot (1/k) \rightarrow 1/(1!) \text{ as } k \rightarrow \infty$$

$$p_{fast}(n, 3) = [(k^2 - k)/2] \cdot (1/k)^2 = (1/2) - (1/(2k)) \rightarrow 1/(2!) \text{ as } k \rightarrow \infty$$

$$p_{fast}(n, 4) = [(k^3 - 3k^2 + 2k)/6] \cdot (1/k)^3$$
$$= (1/6) - (1/(2k)) + 1/(3k^2)) \rightarrow 1/(3!) \text{ as } k \rightarrow \infty$$

$p_{fast}(n, 5) \rightarrow 1/(4!)$ as $k \rightarrow \infty$, and so forth, for n = 1 cycle,

---

* *The French mathematician Blaise Pascal described a triangular arrangement of numbers — now called Pascal's Triangle[2843] — that are useful in algebra and probability theory, in which every number in the interior of the triangle is the sum of the two numbers on either side directly above it:*

1 n = 0
1 1 n = 1
1 2 1 n = 2
1 3 3 1 n = 3
1 4 6 4 1 n = 4
1 5 10 10 5 1 n = 5
1 6 15 20 15 6 1 n = 6

Table 5.4. Replicator population after 20 cycles resulting from several different replication strategies, assuming 1 daughter per generation per replicator

	Replicator Population after n Replication Cycles with τ_{mat}/τ = 2 in first example			
Number of Replication Cycles (n)	**Extended-Maturation Replicators $F_{mat}(n, \tau_{mat}/\tau)$**	**Birth-Immature Replicators $F_{end}(n)$**	**Birth-Mature Replicators P(n)**	**Prenatal-Active Replicators $P_{fast}(n)$**
1	1	1	2	2.7
2	2	2	4	7.4
3	3	3	8	20
4	4	5	16	55
5	6	8	32	148
6	9	13	64	403
7	13	21	128	1097
8	19	34	256	2981
9	28	55	512	8103
10	41	89	1024	22,026
11	60	144	2048	59,874
12	88	233	4096	162,755
13	129	377	8192	442,413
14	189	610	16,384	1,202,604
15	277	987	32,768	3,269,017
16	406	1597	65,536	8,886,111
17	595	2584	131,072	24,154,953
18	872	4181	262,144	65,659,969
19	1278	6765	524,288	178,482,301
20	1873	10,946	1,048,576	485,165,195

whose sum converges to $p_{fast}(n) = 1 + 1/(1!) + 1/(2!) + 1/(3!) + 1/(4!) + \ldots = e = 2.71828\ldots$, for n = 1 cycle. Hence:

$$P_{fast}(n) = [p_{fast}(n)]^n = e^n \qquad \text{(Eqn. 11A)}$$

$$P_{fast}(t) = e^{t/\tau} \qquad \text{(Eqn. 11B)}$$

in the limit as $k \to \infty$, providing another example of exponential growth. Table 5.4 shows the replicator populations resulting from each of the four modes of replication discussed so far: $P_{fast}(n) > P(n) > F_{end}(n) > F_{mat}(n, \tau_{mat}/\tau)$ for n > 3, and after n = 20 replication cycles, $[P_{fast}(20) \sim 10^9] >> [P(20) \sim 10^6] >> [F_{end}(20) \sim 10^4] > [F_{mat}(20, \tau_{mat}/\tau = 2) \sim 10^3]$. Clearly, the choice of replication strategy produces significantly different population growth rates.

So far we have considered only replicators that produce a single offspring during each replication cycle. If each replicator can produce D daughters per generation — i.e., a "litter" of D offspring per pregnancy, rather than just a single daughter per pregnancy — then for birth-mature replicators:*

$$P(n) = (D + 1)^n \qquad \text{(Eqn. 12A)}$$

$$P(t) = (D + 1)^{t/\tau} \qquad \text{(Eqn. 12B)}$$

and for prenatal-active replicators:

$$P_{fast}(n) = D^n \cdot e^n \qquad \text{(Eqn. 13A)}$$

$$P_{fast}(t) = (D \cdot e)^{t/\tau} \qquad \text{(Eqn. 13B)}$$

after n cycles have elapsed, for D > 0, n > 0. While D > 1 gives much higher populations at any given number of cycles than for D = 1, the replication time τ will correspondingly be longer for D > 1 because more mass must be replicated in each cycle. In the simplest case, making twice as many daughters requires replicating twice as much mass, which takes twice as much time at a constant production rate, hence $\tau / \tau_0 \sim D$, where τ_0 is the replication time for D = 1 daughter per litter. In this simple case, Eqns. 12 and 13 predict that the population-maximizing strategy is to minimize the number of daughters, i.e., D = 1 yields the fastest population growth rate. What if the manufacturing time per daughter can be made smaller for additional daughters by some technical means (e.g., "cheaper by the dozen"; see Section 5.9.6)? The population growth-neutral replication time dependency is $\tau_{neutral} / \tau_0 = \log_2(D + 1)$ for birth-mature replicators and $\tau_{neutral} / \tau_0 = 1 + \log_e(D)$ for prenatal-active replicators. That is, if $\tau = \tau_{neutral}$, then choosing any number of daughters per litter gives the same population growth rate. If $\tau > \tau_{neutral}$, as where $\tau / \tau_0 \sim D$ in the simplest case above, then minimizing the number of daughters per litter maximizes the population growth rate. If $\tau < \tau_{neutral}$, then maximizing the number of daughters per litter maximizes the population growth rate. Tradeoffs among these variables should be more systematically investigated.

In the case of the Merkle Cased Hydrocarbon Assembler (Section 4.10.2) where the parental birth-mature replicator is destroyed after each generation is completed, from Eqn. 12A the replicator population is only $P(n) = D^n$ after n generations with D daughters per generation. If a constant time is assumed to be required to assemble each daughter machine and if there is no lag time between completing one cycle and beginning the next one, then the total number of replication cycles N = nD, hence $P(n) = D^{N/D}$. Taking the derivative with respect to D using the general power rule for differentiation, $(\partial/\partial D)P(n) = (1 - \ln(D)) \cdot D^{((1/D)-2)}$ which goes to zero when the replicator population P(n) is maximized. For D > 0, then $(\partial/\partial D)P(n) = 0$ occurs when $1 - \ln(D) = 0$; that is, when $D = e = 2.718\ldots \sim 3$, the optimum number of daughters. (Thanks to C. Phoenix for inspiring this analysis.)

In the case of birth-immature replicators (e.g., Fibonacci rabbits or human beings), Darbro and von Tiesenhausen[1090] report that if

---

** Star Trek's fictional "Tribbles" are furry earless rabbits that are said to be "born pregnant" and to produce a litter of D = 10 offspring every 12 hours,[2844] so three days of unconstrained replication (n = 6) produces a total population of 1,771,561 animals, using Eqn. 12 for birth-mature replicators.*

these replicators are allowed to produce D = 2 pairs of offspring per replication cycle instead of just D = 1 pair of offspring, and keeping $\tau_{mat}/\tau = 1$, then the original "rabbit formula" (Eqn. 4) for total rabbit-pair population $F_{end}(n, D)$ after n replicative cycles becomes:

$$F_{D=2}(n) = [(\phi^{n+2} - (-\phi)^{-(n+2)}) / 5^{1/2}] - 1 \qquad \text{(Eqn. 14)}$$

$$\begin{aligned} F_{end}(n, D) &= F_{D=2}(n + 1) \qquad \text{(Eqn. 15)} \\ &= [(\phi^{n+3} - (-\phi)^{-(n+3)}) / 5^{1/2}] - 1 \quad \text{for } D = 2 \end{aligned}$$

For birth-immature replicators with D > 2, "some similar expressions may be derived [but] they are not so compact";[1090] some formulations have previously been addressed by Hoggatt and Lind.[2845] The authors are unaware of any similar calculations for extended-maturation replicators ($\tau_{mat}/\tau > 1$) with D > 1 that have been published.

Interestingly, a similar set of formulas applies in the financial world, wherein the growth of a given quantity of money is dependent upon the interest rate, "discount" rate, or rate of return. For example, if an initial quantity of money $\$_0$ earns an annual interest rate of i and is allowed to compound $m_\$ \geq 1$ times every year, then the quantity of money after a period of Y years is given by $\$(n) = \$_0 \cdot (1 + i/m_\$)^n$ where $n = m_\$Y$ is the number of compounding periods elapsed. In the case of a 100% annual interest rate, the original money doubles or "replicates" itself in one year if compounded only once ($m_\$ = 1$), so i = 1.00 and $\$(n) = \$_0 \cdot (1 + (1/m_\$))^n = \$_0 \cdot 2^n$ which is equivalent to Eqn. 10 for birth-mature replicators.* In the limit as compounding becomes continuous ($m_\$ \rightarrow \infty$), then $\$(n) = \$_0 \cdot e^n$ which is equivalent to Eqn. 11 for prenatal-active replicators. In a properly functioning capitalist economy, money acts much like a self-replicating entity, with an initial invested amount producing more of itself over time.

5.9.3 Limits to Exponential Kinematic Self-Replication

All of the foregoing scenarios assume that a fecund replicator continues replicating indefinitely — that is, that the replicators are immortal. From a pragmatic engineering perspective it is likely that a fecund replicator will become senescent or damaged after some finite number of replications, or, even if still healthy, might be diverted to nonreplicative activities once the population of replicators has grown large enough. In 1980, both von Tiesenhausen and Darbro[1088,1090] and Valdes and Freitas[1089] examined artificial self-replicating systems in which each replicator device is assumed to produce only a fixed number $\eta_{replica}$ of replicas (constructed at the rate of one daughter per replicative cycle per parent replicator, i.e., litter size D = 1) for a fixed number of generations G, after which time replicative activity ceases and useful production (i.e., nonreplicative activity) begins. In this case, the total population $P(\eta_{replica}, G)$ of replicators at cutoff, when replication stops, is given by:

$$P(\eta_{replica}, G) = (\eta_{replica}{}^{G+1} - 1) / (\eta_{replica} - 1) \qquad \text{(Eqn. 16)}$$

where the number of replication cycles required to reach cutoff is $n = G\ \eta_{replica}$, and the time to reach cutoff is $t_{cutoff} = n\tau$, where τ is the replication time, the units of time required for each replication cycle to be completed.[1088-1090] Figure 5.10 shows a tree diagram of one case of generation-limited replication,[1088] and McCord[1092] has created a matrix notation to efficiently represent the state vector of the generation-limited replicas.

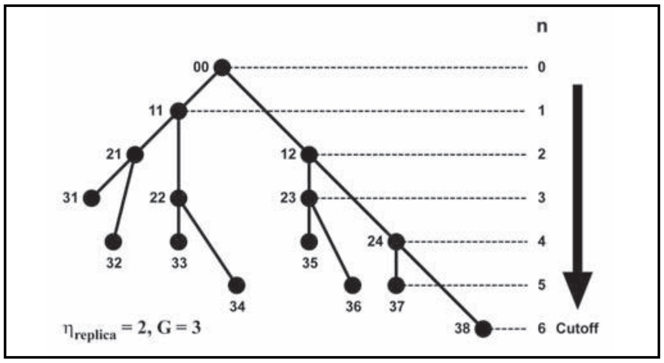


Figure 5.10. Tree diagram of generation-limited replication for $\eta_{replica} = 2$, G = 3. (revised from von Tiesenhausen and Darbro[1088])

We can also examine the limited-replica instance of Eqn. 12, wherein $\eta_{replica} = D$. That is, each replica gets only one pregnancy, produces a single brood of D daughters, and then stops any further replicative activities; each daughter also gets one pregnancy, and so forth. Von Tiesenhausen and Darbro[1088,1090] find that the total population $P_{onebrood}(n)$ after n replicative cycles is given in this case by:

$$P_{onebrood}(n) = (\eta_{replica}{}^{n+1} - 1) / (\eta_{replica} - 1) \qquad \text{(Eqn. 17)}$$

For example, taking $\eta_{replica} = 2$ then after n = 2 replicative cycles, $P_{onebrood}(2) = 7$ because the original replicator has produced two daughters during the first cycle and then ceased further replication, making 3 extant devices, and each of the two daughters subsequently has produced two daughters of their own during the second cycle and then ceased replication, adding 4 granddaughter devices for a total of 7 devices extant. This may be contrasted with the case of unlimited broodnumber assumed for Eqn. 12, which for D = 2 and n = 2 gives P(2) = 9 because the original replicator can produce another two daughters during the second cycle, adding 2 more devices to the previous total of 7.

Continuous exponential growth is only possible for populations of replicators having (1) access to an abundance of material, energy, and information inputs, (2) unrestricted disposal of material and energy outputs so that these outputs will not interfere with replicative activities, (3) no geometric constraints on the positioning or mobility of the physical replicator or any of its external support facilities, and (4) freedom from excessive inherent mortality (i.e., mean replicator lifespan < τ_{mat} or τ), predation, or other programmatic or external restrictions on replication rate or survivability. If replicators are constrained in any of these operational dimensions, then their population may no longer be able to achieve exponential growth and may instead revert to polynomial** or other patterns of growth, or may even cease to grow at all.

** According to one version[2988-2990] of an ancient parable on compound interest, after a wise man performs a useful service for a king in India and the king insists that the man name a reward, the wise man agrees to take one grain of rice for the first square on the king's chessboard on the first day, two grains for the second square on the second day, and so on, doubling the amount daily for all 64 squares of the chessboard. The king, too proud to admit his inability to calculate the sum total of the gift, foolishly grants the wish, at least until it becomes clear that it will wipe out the royal granary (he has committed to deliver 2^{64} = 18,446,744,073,709,551,616 grains of rice or ~1 trillion metric tons, or 2600 times the world production of milled rice in 2002).[2991] Finally, despite his pride the king takes back his repayment, justly embarrassed because of his stupidity and the wise man's obvious generosity in not wanting repayment in the first place. Other versions of this folktale have similar events occurring in China,[2992] Persia, or Japan, and there are darker accounts in which the king is outsmarted by a peasant who is ordered killed when the king discovers his own error.*

*** A power law relates one variable to another raised to a constant power, with the general form of $y = x^a$, where y and x are variables and a is a constant exponent or "power." A polynomial in x is a sum of various powers of x and their positive or negative multiples. The highest power of x which occurs in an equation of growth is called the degree of the polynomial. A polynomial of degree 1 ($y = ax + b$) is called linear; a polynomial of degree 2 ($y = ax^2 + bx + c$) is called quadratic; a polynomial of degree 3 ($y = ax^3 + bx^2 + cx + d$) is called cubic, and so forth. If the polynomial has an infinite number of powers of x whose terms are summed together, it becomes an "exponential" or "power" series. We have seen an example of a power series in Eqn. 11 in which the sum of the series reduces to the general form of $y = a^x$, where y and x are variables and a is a constant base, in this case the natural logarithm e.*

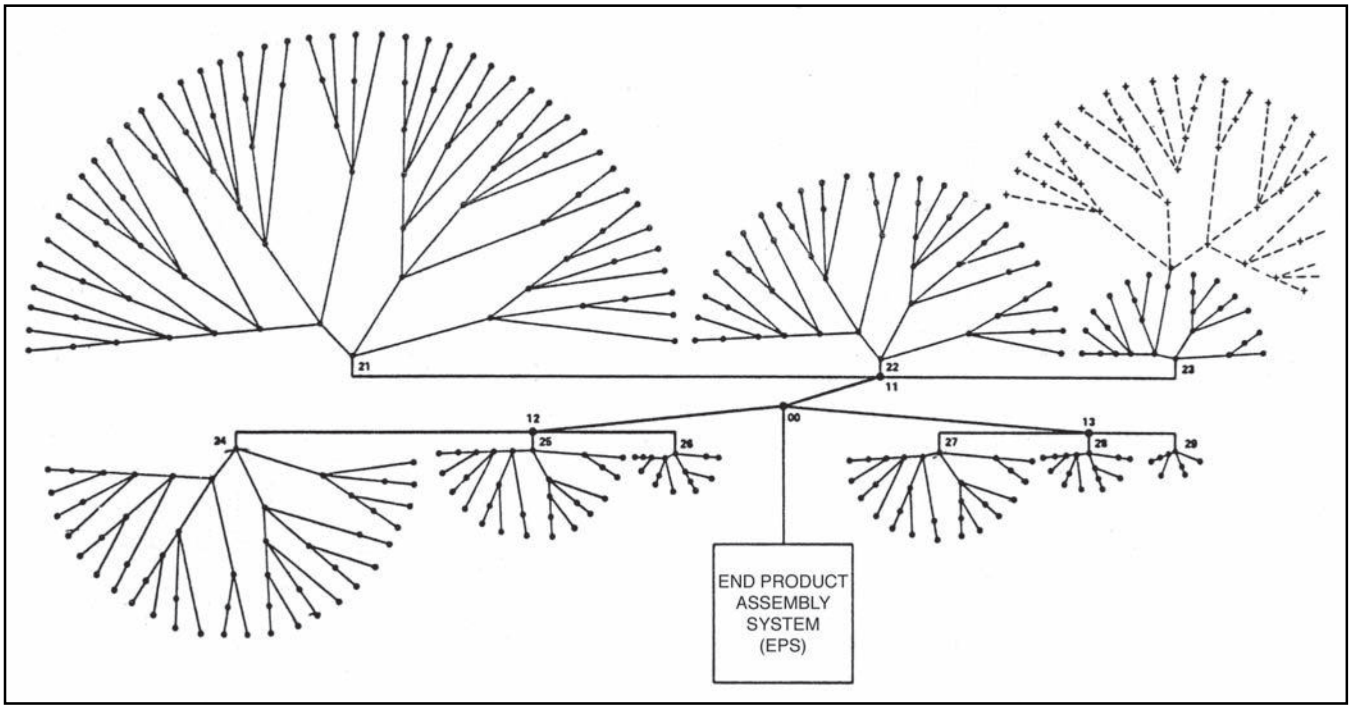


Figure 5.11. Growth plan overview of a field of self-replicating factories on a planetary surface. (courtesy of Georg von Tiesenhausen, NASA/Marshall Space Flight Center)[1088]

For example, exponential growth is not possible for indefinite periods of time on a surface which is the sole fixed source of vital material inputs to a population of replicators (e.g., a lunar factory metabolizing only in situ lunar materials), if population growth occurs via symmetrical radial expansion without shape change or re-siting of units.[1073] Plane surfaces have only a small number of allowed symmetric repetitive structures.[2846] On such surfaces the only possible shapes allowed for contiguous identical units are shapes whose symmetry angles in revolution are 120°, 90°, and 60° – angles given by 360°/p for p = 3, 4, or 6 corresponding to triangular, square, or hexagonal symmetry:[1073] "For these shapes the exponential growth rate $(2)^n$ stops at n = 3, 4, and 5 respectively, where n denotes the number of generations. Once p sides are used up in casting off replicas, no doubling can occur by the unit whose sides are closed off. For a hexagonal SRS (replicator), the sixth side is closed off by neighbor growth before the SRS can produce a sixth replica. Exponential growth on the surface of a planetary body is thus possible only for a few generations. After sufficient generations, replication on a surface can continue only by those replicating systems at the boundary of the SRS population (Figure 3.91). The size of the boundary increases as the square root of the population area and the number of systems, thus the growth is given by a quadratic rule" of the form $P = An^2 + Bn + C$, where P is the total number of self-replicating systems (SRS), n is the number of replicative cycles elapsed, and A, B, and C are constants defined by geometric and replicator design constraints. (Taneja and Walsh[1073] give one example of a 4-fold (adjacent squares) symmetrical layout strategy with A = 2, B = -6, C = 8.) The transition from exponential to polynomial population growth can be postponed by placing initial growth nuclei at numerous well-separated locations (Figure 5.11) so that replicators will not interfere with resource scavenging and other replicative activities of neighboring devices. But as the interior area is filled in, exponential growth is no longer possible as the maximum carrying capacity of the resource environment is approached — replication has become resource-limited.

In population dynamics, this situation is often modeled using a logistic equation of the form:

$$N(t+1) = N(t) \cdot \exp[R_{max} \cdot (1 - (N(t)/K))] \qquad \text{(Eqn. 18)}$$

where N(t) is the number of replicators at time t, R_{max} is the maximum unconstrained population growth rate (net of reproduction and mortality), and K is the maximum replicator carrying capacity of the environment. If $N(t) < K$ and approaches K, growth slows to zero as population rises to a plateau, producing the familiar S-shaped logistic curve.

Freitas (*Advanced Automation for Space Missions*,[2] Section 5.4.4) has also pointed out that no expanding population can disperse faster than its medium will permit, regardless of the speed of manufacture. In the context of a hypothetical far future space exploration program, an expanding spherical population of self-replicating interstellar probes can exhibit exponential population growth of $N(t) = e^{t/\tau}$ if new replicators are produced relatively slowly so that envelope expansion velocity does not constrain dispersal (in which case other constraints will come into play). However, if unit replication is so swift that multiplication is unconstrained by replication time, then the population can grow only as fast as it can physically disperse — that is, only as fast as the expansion velocity of the surface of the spherical outer envelope — or according to:

$$N(t) = (4\pi/3) \cdot d \cdot (Vt)^3 \qquad \text{(Eqn. 19)}$$

where V is peak dispersion velocity for individual replicators at the periphery and d is the number density of useful sites for replication (e.g., uninhabited solar systems). Figure 5.12 shows the transition from exponential to polynomial (a cubic polynomial, in t) population growth when slow (τ = 500 yr) but exponentiating replicators encounter a V = 10% c (c = speed of light) velocity constraint during their expansion; replication in this case is mobility-limited.

Replication can also be mortality-limited, whether intrinsic to the system or externally imposed. For instance, the exponential model of self-replication in population dynamics, commonly associated with Thomas Robert Malthus (1766-1834),[2847] assumes that

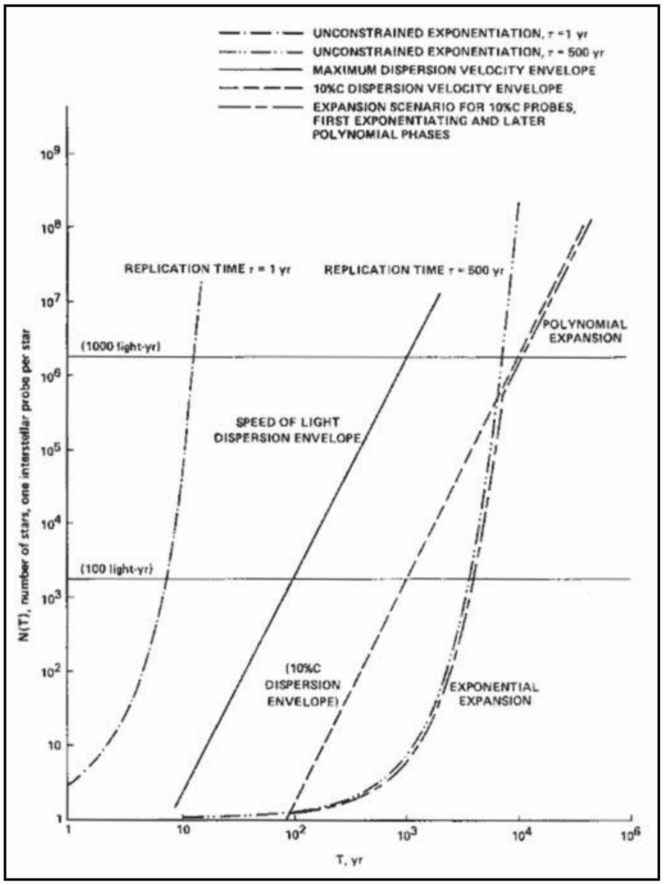


Figure 5.12. Limits to exponential and polynomial expansion of self-replicating interstellar probe populations dispersing throughout the galactic disk. (from Freitas and Gilbreath[2] at Figure 5.24)

replication is continuous (no seasonality), all replicators are identical (no age structure), and environmental resources are unlimited, in which case the replicator population as a function of time is:

$$N(t) = N(0) \cdot e^{Rt} = R \cdot N(t - 1) \qquad \text{(Eqn. 20)}$$

where R = (b – m) is called the Malthusian parameter, the instantaneous rate of natural increase, or the population growth rate. R can be interpreted as the difference between the birth rate (replication) and the death rate (mortality), with birth rate b defined as the number of offspring produced per unit time, per member of the population, and death rate m defined as the number of replicator deaths per unit time, per member of the population. If $R > 0$, the population increases exponentially, but if $R < 0$, the population *declines* exponentially, and if $R = 0$, the population remains constant.

In general, populations of replicators have a basic exponential growth rate given by:

$$(\partial/\partial t)D = k \cdot D^p \qquad \text{(Eqn. 21)}$$

where D is the population density (in population dynamics) or concentration (in chemistry) of the replicating species, k is a growth rate constant, and p = 1 giving exponential growth.[2855]

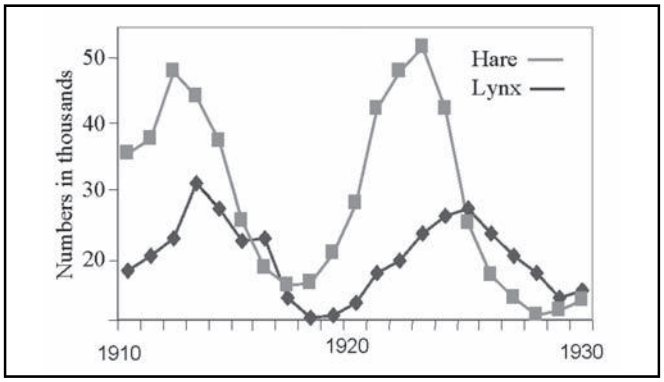


Figure 5.13. Cycles in the population dynamics of the snowshoe hare and its predator the Canadian lynx, redrawn by Radcliffe[2859] from MacLulich.[2857]

Interestingly, some artificial chemical replicating systems exhibit sub-exponential growth ($p < 1$), and, in particular, "parabolic growth" ($p = 0.5$), which was first observed and elucidated by von Kiedrowski and Szathmary.[2848-2855]

Growth in replicator populations can also be severely constrained if two groups of replicators are competing for access to the same resources, or if one group is treating the other group as prey (an input resource). The Lotka-Volterra model[2856] is the simplest model of predator-prey interactions:

$$(\partial/\partial t)D_{prey} = R_{prey} \cdot D_{prey} - a \cdot D_{prey} \cdot D_{predator} \qquad \text{(Eqn. 22A)}$$

$$(\partial/\partial t)D_{predator} = b \cdot D_{prey} \cdot D_{predator} - m \cdot D_{predator} \qquad \text{(Eqn. 22B)}$$

where D_{prey} and $D_{predator}$ are the density of prey and predator, respectively, R_{prey} is the intrinsic rate of prey population increase, a is the predation rate coefficient, b is the replication rate of predators per one prey eaten, and m is the predator mortality rate. When properly parameterized the model can give results that look much like the observed field data of natural populations, such as the cycles in the populations of the Canadian lynx, a predator, and the snowshoe hare, its prey,[2857] as shown in Figure 5.13. Interestingly, similar autonomously oscillating populations of microbes have been observed,[2858] complete with hysteresis, transients, and a constant final frequency, even for single-species populations in the absence of predator-prey relationships.

There is a vast literature on population ecology[2859-2863] — the branch of ecology that studies the structure and dynamics of populations of replicators — that can provide ideas and guidance for future research on various quantitative aspects of machine self-replication in a variety of circumstances. Topics in population ecology typically include density-dependent and density-independent population growth, age and gender distributions, life history strategies,* spatial dispersal patterns, population invasions and diffusion models, optimal foraging and environmental stress,** territory formation[941] and competitive exclusion, predator-prey interactions (prey is food source), parasite-host interactions (host is food source *and* habitat), measures of population entropy[443] or community diversity, experimental evolution[2864] and macroevolution,[482] and so forth — all of which have

---

** There is a generally-accepted[2625,2865] spectrum of strategies between two well-recognized extremes: (1) **r-selection** (high fecundity, rapid development) represents the "quantitative" extreme — in a perfect ecological vacuum with no density effects and no competition, the optimum ecologic strategy is to put all resources into reproduction with the fewest possible resources into each individual offspring, producing as many progeny as possible. (2) **K-selection** (low fecundity, slow development) represents the "qualitative" extreme — when population density effects are maximal and the environment is saturated with competitors, competition is keen so the optimum ecologic strategy is to put all resources into the maintenance and production of a few extremely fit offspring, leading to increasing efficiency of utilization of environmental resources. As a replicator population grows, reproductive strategy may shift from r-selection (maximum intrinsic rate of natural increase) to K-selection (carrying capacity).[2625]*

*** For example, during lean conditions the ratio of replicating individuals to the whole population may be reduced in order to preserve the long-living adults for better future times.[2866]*

their analogs in the design space of mechanical kinematic replicators (Section 5.1.9). However, a complete survey and analysis of the population ecology of machine replicators (e.g., Freitas and Gilbreath,[2] Section 5.5.2) is beyond the scope of this book.

5.9.4 Performance of Convergent Assembly Nanofactory Systems

As previously noted, all replicators are manufacturing systems which accept a stream of inputs and produce a stream of more highly organized outputs, which may include self. Factory-model replicators occupy major portions of the design space (Section 5.1.9) of mechanical kinematic replicators, including replication process centralization (I4), replication process specialization (I5), and the particity of both replicator (D10) and product (K8).

An attractive approach to factory-mode molecular manufacturing is to use convergent assembly[208,213] to rapidly make products whose size is measured in meters starting from building blocks whose size is measured in nanometers. Convergent assembly is based on the idea that smaller parts can be assembled into larger parts, larger parts can be assembled into still larger parts, and so forth. This assembly process can be systematically iterated in a hierarchical fashion,[1569] creating a manufacturing architecture that can span the size range from the molecular to the macroscopic. Of course, in practical systems some provision for error must be made during the assembly of larger parts from smaller parts; Crane[1584] concluded that if imperfect units were cast aside during a hierarchical assembly process, then complex structures could be produced without requiring high accuracy at any step.*

It is common to make bigger things by assembling them from smaller things. A finished assembly which is about 1 meter in size might be made from eight smaller subassemblies each about 0.5 meters in size. The eight subassemblies could be assembled into a finished assembly by using one or more robotic arms (or other positional devices) in assembly modules depicted abstractly in Figure 5.14. Note that we are designating an "assembly module" by the size of its output port. The module size is larger — in this case, the 1.0 meter assembly module has a size of 2.0 meters. This additional size provides sufficient room to handle subassemblies and the final 1.0 meter assembly.

The first module at (A) is a single assembly module able to accept subassemblies from the four input ports to the right, and which produces a finished assembly to the left through the single output port. If the output port has a size of one meter by one meter, each input port would have a size of 0.5 meters by 0.5 meters. The second module at (B) shows two stages of assembly starting with 64 sub-subassemblies each with a size of about 0.25 meters, producing 8 subassemblies with a size of about 0.5 meters, and producing a finished product with a size of about 1.0 meters. The third module at (C) shows three stages of convergent assembly producing a final product of ~1.0 meter in size from 512 sub-sub-subassemblies each of which is ~0.125 meters in size. We can continue adding stages to this process until the inputs to the first stage are as small as we might find convenient. For the purposes of molecular manufacturing, it is easiest to assume that these initial inputs might be ~one nanometer in size — essentially, bulk chemistry inputs.

Now assume that the final 1.0 meter assembly module (A) which assembles the subassemblies into the final product takes about 100 seconds to complete its task. (The exact time selected is not crucial to the conclusions.) Then the 0.5 meter assembly module (B) should complete one subassembly in 50 seconds because an object which is half the size can finish a movement of half the length in half the time: its frequency of operation is doubled.[208] Each 0.5 meter assembly module can therefore produce two subassemblies in 100 seconds, so the four 0.5 meter assembly modules can finish eight subassemblies in 100 seconds, which means that both the 1.0 meter assembly module and the four 0.5 meter assembly modules must work for 100 seconds to produce the final product.

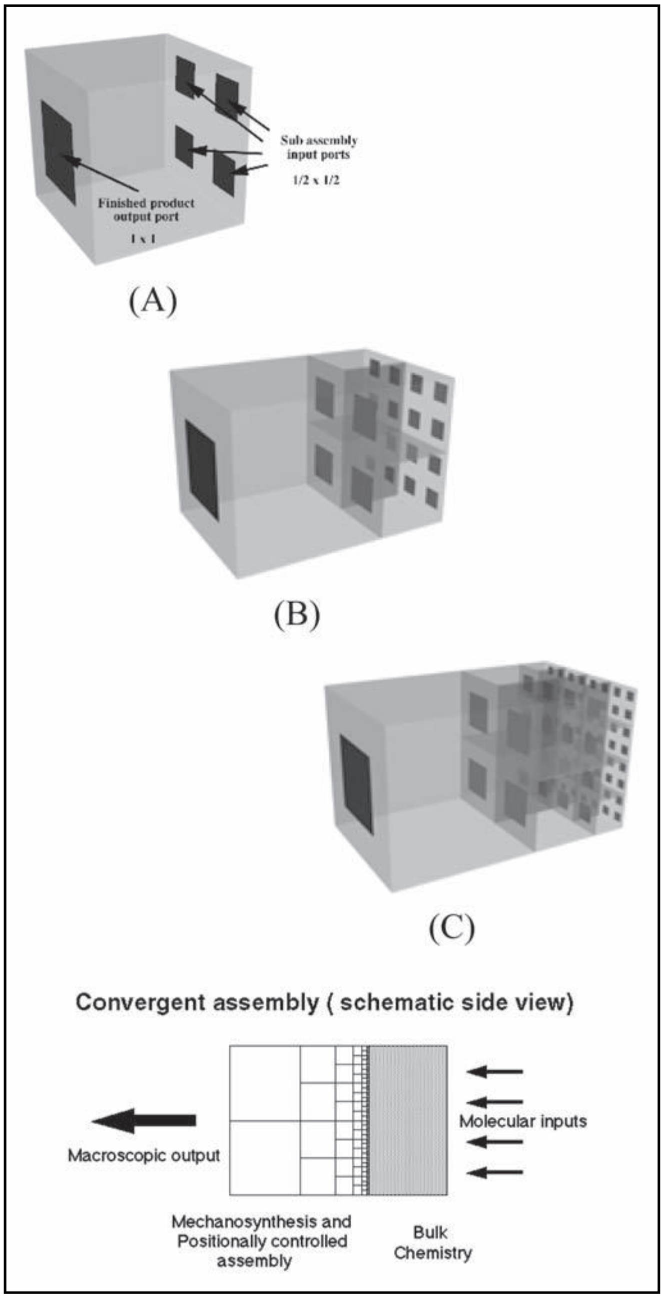

Sub assembly input ports
1/2 x 1/2
Finished product output port
1 x 1
(A)
(B)
(C)
Convergent assembly (schematic side view)
Macroscopic output
Molecular inputs
Mechanosynthesis and Positionally controlled assembly
Bulk Chemistry

Figure 5.14. Progression of assembly modules in convergent assembly, with schematic showing positioning of all modules.[213]

This progression continues in similar fashion for all remaining assembly modules. For instance, at the 0.25 meter assembly module (C) 512 sub-sub-subassemblies are assembled in sixteen 0.25 meter assembly modules, making 64 sub-subassemblies; these 64 sub-subassemblies are assembled into 8 subassemblies in four 0.5

---

* *But T. Hogg[856] notes that there is a tradeoff in efficiency: if the discard rate is too high, the rate of final production will be very low. Typically such situations have a fairly abrupt threshold in the probability of success vs. individual defect rate, as seen in studies of molecular electronics circuits formed via self-assembly for multiplexors and logic circuits.[1554] Simon[2867] has also discussed both natural and artificial modular structures.*

meter assembly modules, and finally, the 8 subassemblies are assembled into the final product in the single 1.0 meter assembly module. Again, the 0.25 meter assembly modules operate twice as fast as the 0.5 meter assembly modules, and four times as fast as the 1.0 meter assembly module. The sixteen 0.25 meter assembly modules can make 64 sub-subassemblies in the same time that the four 0.5 meter assembly modules can make 8 subassemblies, which is the same amount of time that the single 1.0 meter assembly module takes to produce the finished product, thus establishing throughput closure (Section 5.6).

The following rules (modified and extended from Merkle[213]) hold approximately for a convergent assembly system which doubles the size of product made at each stage, starting with initial building blocks of characteristic length L_{block} meters (e.g., $L_{block} \sim 10^{-9}$ meters, or one nanometer) with a characteristic assembly time to manipulate those building blocks of t_{block} (e.g., $t_{block} \sim 10^{-7}$ seconds, or 100 nanoseconds) in an actual manufacturing system:

1. **Product Size**. The size of product that can be made at stage N is:

   $$L_{product}(N) = 2^N \cdot L_{block} \text{ (meters)} \qquad \text{(Eqn. 23)}$$

   and conversely, the number of stages required to make a product of size $L_{product}$ from starting blocks of size L_{block} is:

   $$N(L_{product}) = \log_2(L_{product}/L_{block}) \text{ (stages)} \qquad \text{(Eqn. 24)}$$

   Hence the assembly of a product object of size $L_{product} = 1$ meter using building blocks of size $L_{block} = 10^{-9}$ meter requires a convergent assembly system (using this particular architecture) consisting of $N(L_{product}) = \log_2(1/10^{-9}) \sim 30$ stages.

2. **Module Assembly Time**. The time required for an assembly module in the Nth stage to produce an assembly of size $L_{product}(N)$ ($= 2^N \cdot L_{block}$) meters, given that eight subassemblies of size $2^{(N-1)} \cdot L_{block}$ meters are already available, is:

   $$t_{module} = 2^N \cdot t_{block} \text{ (seconds)} \qquad \text{(Eqn. 25)}$$

   The exemplar values chosen for t_{block} and L_{block} imply that the assembly of a 1.0 meter product (i.e., stage N = 30) from eight 0.5 meter subassemblies (i.e., stage N = 29) will require $t_{module} = 2^N \cdot t_{block} = 2^{30} \cdot (10^{-7} \text{ sec}) \sim 100$ seconds. We assume that the assembly process can be started when only four subassemblies are available, effectively allowing stage N to begin operation after stage (N – 1) has produced only half of the required subassemblies.

3. **Product Assembly Time**. The time required to build a product of size $L_{product}$ ($= 2^N \cdot L_{block}$) meters, including the time taken by all preceding stages (i.e., assuming all stages start empty, with no assemblies or subassemblies in them, but that they have been provided with appropriate instructions for the manufacture of the desired product) is:

   $$t_{product} = 2^{(N+1)} \cdot t_{block} \text{ (seconds)} \qquad \text{(Eqn. 26)}$$

   This is because the assembly modules at stage (N – 1) produce their first output in $2^N \cdot t_{block}$ seconds, whereupon the assembly process begins in stage N; the assembly process in stage N must then continue an additional $2^N \cdot t_{block}$ seconds before it can produce its first output, so the total time before stage N produces an output is $(2^N + 2^N) \cdot t_{block}$ seconds or $2^{(N+1)} \cdot t_{block}$ seconds. Thus a 30-stage system (N = 30) should be able to produce a single meter-sized product in ~200 seconds. If we more conservatively assume that stage N cannot overlap any operations at all with stage (N – 1) — that is, stage (N – 1) must produce all eight subassemblies before stage N can begin to assemble them — then the time required for the Nth stage to produce its first output increases from $2 \cdot 2^N \cdot t_{block}$ seconds to $3 \cdot 2^N \cdot t_{block}$ seconds, only 50% longer, or ~300 seconds to produce a single meter-sized product in a 30-stage system with this exemplar architecture.

4. **Production Rate**. A convergent assembly system can be pipelined, in which case a steady stream of finished products of size $L_{product}$ ($= 2^N \cdot L_{block}$) meters can be made at a rate of one new product every $2^N \cdot t_{block}$ seconds, a production rate of:

   $$R_{production} = (2^N \cdot t_{block})^{-1} \text{ (products/sec)} \qquad \text{(Eqn. 27)}$$

   $$\text{with} \quad t_{pipeline} = R_{production}^{-1} \qquad \text{(Eqn. 28)}$$

   Thus a 30-stage system (N = 30) should be able to build a steady stream of meter-sized products at the rate of ~1 new product every 100 seconds, giving a production rate of $R_{production} \sim 0.01$ products/sec (e.g., $t_{pipeline} = 100$ sec/product) with this exemplar architecture.

5. **Output Port Areas**. The area of the output port $A_{output}(N)$ of an assembly module equals the sum of the areas of each input port $A_{input}(N)$; that is:

   $$A_{input}(N) = 2^{2(N-1)} \cdot L_{block}^2 \text{ (meter}^2\text{)} \qquad \text{(Eqn. 29)}$$

   $$A_{output}(N) = \Sigma\, A_{input}(N) = 2^{2N} \cdot L_{block}^2 \text{ (meter}^2\text{)} \qquad \text{(Eqn. 30)}$$

   The total area of all output ports throughout the factory at stage N is equal to the total area of all output ports throughout the factory at stage (N – 1).

6. **Materials Throughput Speed**. The average speed with which material flows through the system is approximately equal at all stages, given by:

   $$v_{materials} \sim L_{block} / t_{block} \text{ (meters/sec)} \qquad \text{(Eqn. 31)}$$

   For $L_{block} \sim 10^{-9}$ m and $t_{block} \sim 10^{-7}$ sec, $v_{materials} \sim 1$ cm/sec.

7. **Materials Flowthrough Path Length**. Since the input material is in motion through the factory for $t_{motion} = 2^N \cdot t_{block}$ seconds, then these materials travel a path length of:

   $$L_{path} \sim v_{materials} \cdot t_{motion} \text{ (meters)} \qquad \text{(Eqn. 32)}$$

   For $v_{materials} \sim 1$ cm/sec and $t_{motion} = 100$ sec, $L_{path} \sim 1$ meter.

8. **Convergent Assembly Factory Length, Volume, and Replication Time.** Taking the width (and height) of the final assembly module output face as $2L_{product}$ and the length of the Nth stage as $2L_{product} \cdot (1/2)^{N-1}$, then the minimum length and volume of the convergent factory are given by:

   $$\begin{aligned} L_{factory} &= 2L_{product} \cdot \sum_{i=1}^{N(L_{product})} (1/2)^{i-1} \\ &= 4L_{product} \cdot (1 - (1/2)^{N(L_{product})}) \qquad \text{(Eqn. 33)} \end{aligned}$$

   $$V_{factory} = (2L_{product})^2\, L_{factory} \qquad \text{(Eqn. 34)}$$

   Assuming that 8 product objects each of volume $L_{product}^3$ can be assembled to make a complete factory of volume $V_{factory}$, then the replication time for a fully pipelined convergent assembly factory is given by:

   $$\begin{aligned} \tau_{factory} &= t_{pipeline} \cdot V_{factory} / L_{product}^3 \\ &= 16\, t_{pipeline}\, (1 - (1/2)^{N(L_{product})}) \qquad \text{(Eqn. 35)} \end{aligned}$$

   Taking $L_{product} = 1$ meter, $L_{block} = 10^{-9}$ meter, and $t_{block} \sim 10^{-7}$ seconds, then $N(L_{product}) = 30$ stages (from Eqn. 24), $t_{pipeline} \sim 100$ sec (for N = 30, from Eqn. 28), $L_{factory} \sim 4$ meters, $V_{factory} \sim 16$ meter^3, and $\tau_{factory} \sim 1600$ sec (~1/2 hour). Note that for N >>1, $\tau_{factory} \sim (2^{N+4}) \cdot t_{block}$.

Other methods for quantitatively estimating bootstrapping productivity or self-replicating factory output in various contexts have been employed by Akin and Minsky [964], Bock [2688], Criswell,[953] Hall,[225] Hewitt,[957] Lackner and Wendt,[1128] McKendree,[973-975] Phoenix,[2334] and Miller and Smith.[2689]

5.9.5 Power Law Scaling in Convergent Assembly Nanofactory Systems

J. Storrs Hall has made an interesting observation concerning a discrepancy in the power law scaling of convergent assembly nanofactories as compared with biological systems, and has produced a mathematical analysis[2868] from which the following discussion is drawn extensively.

As noted in Section 5.9.4, one of the standard architectures for a molecular manufacturing system (*Nanosystems*[208] at Section 14.3.1.b) is convergent assembly, in which a very large array of very small manufacturing machines makes molecular-scale parts, after which a second array of not-quite-as-small manufacturing machines puts parts together into bigger parts, and so forth. At each stage the number of manufacturing machines decreases by some fraction, and the size of the parts increases by some fraction. For example, in the proposal by Merkle[213] (Section 5.9.4) a cubical system accepts inputs from 4 half-size (1/8 volume) precursor cubical systems. The half-size cubes run twice as fast as the big ones — the product moves through them at the same absolute speed but only has to go half as far — and the 4 half-size cubes feed 8 subassemblies to the full-size cube in the time required for the full-size cube to produce one output assembly. Each smaller cube is in turn fed by 4 smaller cubes, and so forth. Adding a new stage of double the size increases system mass M_{system} by a factor of 8. But since the new stage includes only four cubes of the prior stage, output has only increased by a factor of 4, so the time (τ) the new system takes to produce its own mass in output is twice as long as the old one. This is called a one-third power scaling law of replication time to mass — that is, replication time is proportional to the cube root of the mass, i.e., $\tau \sim M_{system}^{1/3}$.

Hall[2868] shows that any strictly self-similar convergent assembly nanofactory system in which each stage is a scale model of the next, and where the same scale factor (and thus the same mass ratio) applies to all stages, must also have a one-third power scaling law. To demonstrate this, and as a generalization of the case examined in Section 5.9.4, Hall considers a system with a branching factor of n in units of mass of a (k)-stage system. If x is the mass of the (k + 1)-stage node, then the mass of the full (k + 1)-stage system is (n + x) and so the mass ratio of a (k + 1)-stage system to a (k)-stage system is (n + x). Using the time to replicate a k-stage system as the unit of time, the output per unit time of a (k + 1)-stage system is n, hence the time to replicate for a (k + 1)-stage system is $\tau_{k+1} = (n + x) / n$. The mass ratio of the (k + 1)-stage node to the k-stage node is also (n + x): The ratio of the head node to the whole system is x / (n + x), which equals the ratio of the k-stage node to the whole subsystem it is the head of; but since that is 1 by definition, then the mass of a k-stage node is just x / (n + x), so the ratio of the (k + 1)-stage node to the k-stage node is x / (x / (n + x)) = (n + x).

For a power scaling law in 1/Z of the form $\tau \sim M_{system}^{1/Z}$, the replication time raised to the power Z equals the mass ratio, that is, $\tau^Z = ((n + x) / n)^Z = (n + x)$, which, after a series of algebraic manipulations, yields in turn: $(n + x)^{(Z-1)} / n^Z = 1$, $(n + x)^{(Z-1)} = n^Z$, $(n + x) = n^{(Z/(Z-1))}$, therefore $x = n^{(Z/(Z-1))} - n$, or $(n + x) = n^{(Z/(Z-1))}$. Because of strict scaling, the area of the output port on any node scales with the area of a side, and since the flow of material out of a node must equal the total flow into it, then $(n + x)^{2/3} = n$ or $(n + x) = n^{3/2} = n^{(Z/(Z-1))}$, and Z = 3. Thus Z must equal 3 for any strictly self-similar convergent assembly nanofactory system, i.e., such systems must have a one-third power scaling law of replication time to mass.

The discrepancy with biology occurs because natural systems, like animals and plants, empirically have a well-documented one-fourth power (Z = 4) scaling law for replication time (Section 5.2), believed to be related to the fractal nature of vascular and similar systems. In other words, if replicator system mass increases by a factor of 1000, replication time rises by a factor of 10 for a convergent-assembly nanofactory having Z = 3 but only by a factor of 5.62 for biological replicators having Z = 4. Hall's contribution is his insight that, in principle, convergent-assembly nanofactories can also achieve one-fourth power (Z = 4) scaling, matching biological systems, if the length of units is allowed to scale by one factor (L) while the radius, incorporating the other two spatial dimensions, is allowed to scale by a different factor (R). In this case the mass ratio becomes $L \cdot R^2 = (n + x)$; Z = 4 implies that $(n + x) = n^{4/3}$, fixed output area implies that $R^2 = n$, therefore $L = (n + x) / R^2 = n^{4/3} / n = n^{1/3}$.

One simple nanofactory design following the new rules allowing Z = 4 is to let n (the branching factor) equal 2, producing a binary tree structure with $L = 2^{1/3}$ and $R = 2^{1/2}$. The design (Figure 5.15) is a fractal plumbing embedded in a box with relative dimensions $1 \times 2^{1/3} \times 2^{2/3}$. This box can be recursively divided in half, by running in a pipe from the center of a large side and slicing to halve the long dimension, giving two boxes similar to the first one. The pipes decrease in length by a factor of $L_{k-1}/L_k = n^{-1/3} = 2^{-1/3} = 0.7937$ and decrease in radius by a factor of $R_{k-1}/R_k = n^{-1/2} = 2^{-1/2} = 0.7071$. However, cautions Hall: "It remains to be seen whether we can design actual assembly machinery along these lines."

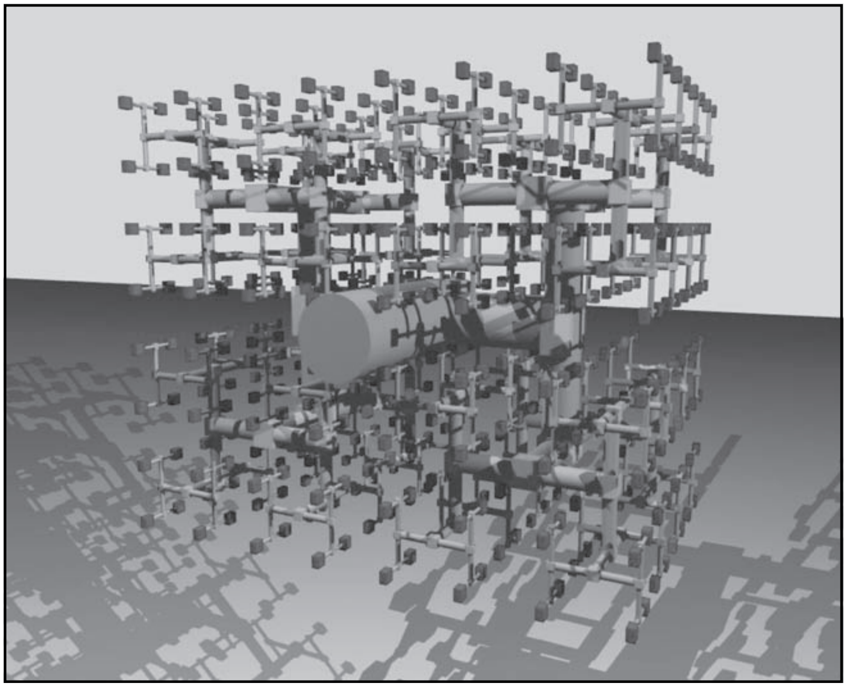


Figure 5.15. Geometry for a convergent-assembly nanofactory system with a one-fourth power scaling law. (image courtesy of J. Storrs Hall[2868])

5.9.6 Design Tradeoffs in Nanofactory Assembly Process Specialization

The specialization of active subunit components within a replicator system seems likely to increase manufacturing throughput rates as compared to systems having only general-purpose active subunits, though probably at the cost of reduced flexibility.[208] As we saw in Section 5.9.2, allowing increasing numbers of active subcomponents to contribute immediately to replication processes improves the growth rate from $P(t) = 2^{t/\tau}$ (Eqn. 10B) to a maximum of $P_{fast}(t) = e^{t/\tau}$ (Eqn. 11B). In effect, the division of a single general-purpose replicator working mass of a particular type into the maximum possible number of more-specialized working sub-masses of the same particular type increases replicator productivity by up to a factor of $(e^1/2^1) = 1.359$ per generation in the limit, an amount that grows to a $(e^{20}/2^{20}) = 463$ fold advantage in the limit by the 20th generation (Table 5.4), a substantial improvement. This assumes that a significant amount of total manufacturing time is utilized in increasing the total manufacturing capacity, rather than in making nonreplicating (non-self) product outputs.

Another estimate, inspired by an analysis by Hall[225] but using more conservative assumptions, can compare the benefits of specialization using replicating systems having components of two different particular types — for example, mill-type mechanisms and manipulator-type mechanisms. As noted earlier (Section 5.1.9 (H6)), with one set of assumptions, specialized mill-type mechanisms may be ~40 times more productive per unit mass than manipulator-type mechanisms, although manipulator systems are far more versatile or "general purpose" than mill systems. So it is logical to presume that a replicating system composed entirely of mill-type mechanisms, using similar assumptions, should be ~40 times more productive per unit mass than a replicating system composed entirely of manipulator-type mechanisms.

Accordingly, let us consider two possible self-replicating systems, one that is "specialized" and another that is "general-purpose." The **specialized factory** consists of molecular mills (Figure 4.35) that may include separate assembly lines specialized for gears, pulleys, shafts, bearings, motors, struts, pipes, self-fastening joints, and so forth. Its architecture also includes conveyors and a tiny number of general-purpose manipulators for putting the final parts together (which are few enough that we can ignore them in the calculation). The **general-purpose factory** consists exclusively of some number of general-purpose programmable robotic arm manipulators of the kind described by Drexler (Figure 4.29), with no specialized molecular mills included. We will estimate the time t_{macro} required for each system to grow large enough to be capable of producing macroscale products, a capacity threshold which Hall[225] arbitrarily defined as the ability to do $R_{macro} = 10^{20}$ mechanosynthetic atom-deposition reactions per second (~0.5 mm³/sec of solid diamond crystal), starting from a much smaller initial seed system.

Consider first the **specialized replicating system** of molecular mills. If:

N_{MILLa} is the number of atoms per individual mill assembly mechanism,
n_{atomM} is the number of atoms deposited by each mill assembly mechanism per operating cycle,
$x_{station}$ is the distance separating individual mill mechanisms along the conveyor belt,
$V_{conveyor}$ is conveyor belt speed,
N_{PARTSa} is the number of atoms in a typical part,
$n_{parttypes}$ is the number of different kinds of typical parts used to build the specialized replicating system, and
q is a constant which multiplies the number of atoms in the core replicator system, to allow for external support structure and "overhead" for fully pipelined parts assembly,

then the productivity of all specialized mill mechanisms is $R_{millS} = n_{parttypes} \cdot N_{PARTSa} \cdot V_{conveyor} / x_{station}$ (atoms/sec), the number of individual mill mechanisms per part type in the initial seed system is $n_{mills} = N_{PARTSa} / n_{atomM}$, and the replication time of the initial seed system is $\tau_{millS} = q \cdot (n_{mills} \cdot N_{MILLa} / N_{PARTSa}) / (V_{conveyor} / x_{station})$, hence the time required for the specialized system to grow to macroscale capacity is $t_{macroS} = \tau_{millS} \cdot G_{millS}$ (generations) where $G_{millS} = \log_{10}(R_{macro} / R_{millS}) / \log_{10}(2)$, or:

$$t_{macroS} = \frac{q \cdot n_{mills} \cdot N_{MILLa} \cdot x_{station}}{\log_{10}(2) \cdot N_{PARTSa} \cdot V_{conveyor}} \cdot \log_{10}\left(\frac{R_{macro} \cdot x_{station}}{n_{parttypes} \cdot N_{PARTSa} \cdot V_{conveyor}}\right) \qquad \text{(Eqn. 36)}$$

and the total number of atoms in the initial seed system is:

$$N_{seedSa} = q \cdot n_{parttypes} \cdot n_{mills} \cdot N_{MILLa} \text{ (atoms)} \qquad \text{(Eqn. 37)}$$

Taking q = 2 (Hall[225]), n_{atomM} ~ 1 atom/mill (*Nanosystems*,[208] Section 13.2.3; Hall[225]), $N_{MILLa} = 2.5 \times 10^5$ atoms/mill mechanism (*Nanosystems*,[208] Section 13.3.5.c), $x_{station} = 10$ nm (*Nanosystems*,[208] Section 13.3.1.a; Hall[225]), $N_{PARTSa} = 10^4$ atoms/part (Hall[225]), $V_{conveyor} = 0.005$ m/sec (*Nanosystems*,[208] Section 13.3.1.a), $R_{macro} = 10^{20}$ atoms/sec (Hall[225]), and $n_{parttypes} = 100$ (Hall[225]), then $R_{millS} = 5 \times 10^{11}$ atoms/sec, $n_{mills} = 10^4$ mills/part type, $\tau_{millS} = 1$ sec and $N_{seedSa} = 5 \times 10^{11}$ atoms in the initial seed system, with $t_{macroS} = 28$ seconds to replicate $G_{millS} = 28$ doubling generations of the initial seed system to reach the threshold of macroscale manufacturing output.

Consider next the **general-purpose replicating system** of manipulator arms. If:

N_{ARMa} is the number of atoms per individual manipulator arm assembly mechanism,
t_{motion} is the time required to execute one full manipulator arm motion pathlength,
n_{motion} is the number of full manipulator arm pathlength motions needed to deposit one atom, and
N_{seedGa} is the total number of atoms in the initial seed system,

then the number of individual arm mechanisms in the initial seed system is $n_{arms} = N_{seedGa} / N_{ARMa}$, the productivity of all general-purpose manipulator arm mechanisms in the seed system is $R_{armG} = n_{arms} / (t_{motion} \cdot n_{motion})$ (atoms/sec), and the replication time of the initial seed system is $\tau_{armG} = q \cdot N_{seedGa} / R_{armG}$, hence the time required for the specialized system to grow to macroscale capacity is $t_{macroG} = \tau_{armG} \cdot G_{armG}$ (generations) where $G_{armG} = \log_{10}(R_{macro} / R_{armG}) / \log_{10}(2)$, or:

$$t_{macroG} = \frac{q \cdot N_{ARMa} \cdot t_{motion} \cdot n_{motion}}{\log_{10}(2)} \cdot \log_{10}\left(\frac{R_{macro} \cdot N_{ARMa} \cdot t_{motion} \cdot n_{motion}}{N_{seedGa}}\right) \qquad \text{(Eqn. 38)}$$

Taking q = 2 (Hall[225]), $N_{ARMa} = 10^7$ atoms/arm (*Nanosystems,*[208] Section 13.4.1.f; Hall[225]), $t_{motion} = 10^{-6}$ sec per 10-nm motion (*Nanosystems*,[208] Section 13.4.1.f), $n_{motion} = 2$ motions per atom deposition (one motion from tool recharge to workpiece plus one motion from workpiece to tool recharge), $R_{macro} = 10^{20}$ atoms/sec (Hall[225]), and $N_{seedGa} = N_{seedSa} = 5 \times 10^{11}$ atoms (to permit easy comparison with a mill-based system of exactly equal size), then $n_{arms} = 5 \times 10^4$ manipulator arms, $R_{armG} = 2.5 \times 10^{10}$ atoms/sec, and $\tau_{armG} = 40$ sec in the initial seed system, with $t_{macroG} = 1276$ seconds to replicate $G_{armG} = 32$ doubling generations of the initial seed system to reach the threshold of macroscale manufacturing output. (Note also that $N_{ARMa} / N_{MILLa} = 40$.)

Thus, as expected, the specialized system can replicate τ_{armG} / τ_{millS} = 40 times faster* than the comparably-sized general-purpose system and also allows faster build-out (e.g., t_{macroG} / t_{macroS} = 46) and higher throughput rates (e.g., R_{millS} / R_{armG} = 20), but at the cost of losing virtually all programmable variation in the building blocks and block assemblies which are exclusively assembled by mill mechanisms. It should be easier to have newly manufactured subcomponents contributing immediately in a nanofactory consisting of robot arms since each arm could be set to work on whatever job was to be done next, while a newly-built special-purpose mill would have to wait for its companion mills to be finished (and connected together) before it could start making products.

Adds Drexler:[208] "Manipulator-style mechanisms will tend to have lower stiffness and hence higher error rates than those of mill-style mechanisms. Nonetheless, the feasible stiffness permits errors stemming from thermal excitation to be kept to negligible levels. Manipulators under programmable control can more easily be designed for fault tolerance than can mill systems." Functionally-specialized systems also have the potential drawback of requiring separate design, construction, and testing for each of two or more specialized machines (even if individually less complex), rather than just one general-purpose machine, and are almost certainly more constrained in the range of different products they can produce (compared to a single more general-purpose assembler).

Analogously in the field of pure computation, the GRAPE computer family (with its specialized hardware chips for efficiently calculating Newtonian gravitational force between particles in computational astrophysics[2869]) and IBM's Deep Blue chess-playing computer (with its specialized chess-move calculation hardware chips[2870]) have shown greater speed at one narrow task but have far less versatility** than a more general-purpose parallel computer with comparable gross hardware specifications. There is evidence that flexible "reconfigurable computing"[2871] may be superior to fixed-path hardware in many applications (e.g., see the "Embryonics project" in Section 2.2.1). In the field of manufacturing, automakers in Detroit and elsewhere have steadily moved away from single-process manufacturing on their automobile assembly lines, in favor of flexible manufacturing systems (using manufacturing robots more akin to manipulators than to mills) that allow different products to be produced on the same production line and that also allow rapid switching between products.

Finally, readers are reminded that there are many ways to operationalize component and active subunit specialization. One way is via a "factory production line" approach with specialized sub-lines, as in Drexler's desktop assembler (Section 4.9.3) or Hall's factory replication architecture (Section 4.16). Another way is by using specialized individual replicator devices, as in Freitas' biphase assembler (Section 4.18). Both approaches reap the benefits of process specialization while employing utterly different architectures. Also, when discussing "production lines" vs. "replicators" it is important to clearly distinguish the concept of component function specialization (i.e., "Replication Process Specialization" or dimension "I5" in the replicator design space described in Section 5.1.9) from other temptingly-similar and seemingly-related dimensions in the replicator design space with which I5 is frequently confused or conflated, such as Replication Process Centralization (I4), Replication Process Subunit Assistance (I8), Replication Auxeticity (I11), and Replication Process Parallelicity (I13).

5.10 Replicators and Artificial Intelligence (AI)

The possible creation of a machine-based human-equivalent or human-different artificial intelligence (AI) — whether deliberately built or emergent — has been described in the technical scientific,[912,2872-2884] popular scientific,[2886-2891] and science fiction[2892-2898] literatures for many decades. True human-equivalent computing is conservatively estimated to require a computational capacity on the order of 10-1000 teraflops ($\sim 10^{13}$-10^{15} floating-point operations/sec),[2884-2887] though various estimation methods can produce a somewhat wider range of values (10^{12}-10^{17} ops/sec).[2887,2912-2914] (IBM's $\sim 10^{12}$ ops/sec Deep Blue parallel computer defeated human grandmaster Gary Kasparov at chess in 1997.)[2870] These bit rates are many orders of magnitude higher than the data processing requirements of all classes of contemporary industrial manufacturing machines, and also well beyond most estimates of the computational capacities needed to drive future autonomous nanorobotic devices. For example, artificial nanorobotic red cells (respirocytes[229]) may require no more than a simple $\sim 10^3$ ops/sec computer — far less computing power than an old Apple II machine — while nanorobotic white cells (microbivores[233]) may need only $\sim 10^6$ ops/sec of onboard capacity. Still more sophisticated cellular repair nanorobots should demand no more than 10^6-10^9 ops/sec of onboard computing capacity to do their work (*Nanomedicine*,[228] Section 7.1), a full 4-9 orders of magnitude below the estimates for true human-equivalent computing.

Similarly, estimates of the data storage capacity of the human brain have ranged from a low of ~200 megabytes (1.6×10^9 bits) for consciously-recoverable data,[2915] to a range of 10^{13}-10^{15} bits based on an assumption of ~1 bit per synapse,[2885,2916,2917] to upper limits of 2.2×10^{18} bits for the information contained in a lifetime of experience (brain inputs)[2885,2913,2918] or 10^{20} bits based on the accumulated total of all neural impulses conducted within the brain during a lifetime.[2919] (One recent estimate[2920] of 10^{8432} bits for total human memory seems wildly implausible.) By contrast, Table 5.1 shows that a wide variety of mechanical, software, and biological replicators require at most 10^2-10^{12} bits for the storage of their description, and the actual number is likely to be considerably less. For example, the self-replicating DNA sequence that describes the human phenotype is nominally 6×10^9 bits,[2487] but there is a great amount of repetition (such as the 300,000 "ALU" sequence repeats) so the data may compressible by at least 100:1 if the noncoding regions are greatly condensed or eliminated, reducing the bit count to under $\sim 10^8$ bits — or 2-12 orders of magnitude smaller than the storage capacity required to store a human-level intelligence. The number of data bits needed to support an artificial intelligence seems to be many orders of magnitude larger than the number of bits that are likely required to support an artificial replicator.

In the 1970s, Carl Sagan[2921] quoted AI expert Marvin Minsky as claiming that as few as 10^6 bits might be enough to encode an artificially-designed "true intellect" — provided the bits "were all in the right place....I cannot conceive that it would take 10^{12} bits to hold a superintelligent being."* (The 2003 release of Microsoft Windows requires ~2.4 x 10^{10} bits of storage — 50 million lines of code averaging 60 characters/line at 8 bits per character.) By comparison, the simplest-known software replicators require only 16-808 bits to encode (depending on one's definitions; Section 2.2.1 and Table 5.1), so it would seem that replicators may be at least 3-5 orders of magnitude simpler than intelligences, even if Minsky is correct.

---

* *These results are largely insensitive to the exact choice of R_{macro} and $n_{parttypes}$ but are highly sensitive to the choice of $V_{conveyor}$, N_{PARTSa} and t_{motion}. Drexler suggests that specialized mills and general-purpose manipulators might even have comparable replication times for some choices of parameters, e.g., $\tau \sim 3$ sec for mills (*Nanosystems,*[208] Section 13.3.5.d) and $\tau \sim 5$ sec for manipulators (*Nanosystems,*[208] Section 13.4.1.f). There are additional limits to convergent assembly processes based on power and heat generation, and different types of defect mechanisms at different scales.[208] A more comprehensive analysis should be performed but is beyond the scope of this book.*

** *The implications of using manufacturing components functionally analogous to the reconfigurable logic as found in Field-Programmable Gate Array (FPGA) technology should be investigated further in the context of flexible nanomanufacturing and specialization.*

In other words, replication appears to be a rather simple activity when compared to intelligence. We conclude that artificial replicators are likely to require many orders of magnitude less memory and data processing capacity than an artificial intelligence, hence are unlikely to incorporate an onboard artificial intelligence unless the inclusion of an AI is a principal design objective. Indeed, common computer viruses and worms are examples of artificial software replicators (Section 2.2.1) and are typically small in size (a few kilobytes). Adding an AI to a replicator would greatly increase the complexity and design difficulty of building a replicator, and would also increase the risks to public safety (Section 5.11). If emergent AIs prove easier to create than deliberately-built AIs, e.g., by using genetic algorithms, then the risk to public safety is again increased.[2898] Non-AI replicators are vastly simpler to design and build (and will be much safer to operate) than artificial intelligence based replicators. As technology progresses, it is likely that basic multifunctional replicators can be built long before an AI can be built, and that at least the earliest generations of artificial replicators will contain no onboard AI. Our conclusion is supported by the observation that in the evolution of life on Earth, the first replicators may have appeared only ~0.8 billion years[2924,2925] after the planet's formation but another 3.5-3.85 billion years[2924-2926] of further evolution were required for human-level intelligence to emerge,[2927] employing the same organic substrate.

5.11 Replicators and Public Safety

It has been pointed out that the development and deployment of artificial replicators capable of unconstrained replication using the natural environment as substrate would raise serious public safety and environmental concerns.[199,2908-2911] Perhaps one of the earliest scientists to voice this concern was Freeman Dyson, who opined, in a 1972 lecture,[2934] that:

> *I assume that in the next century, partly imitating the processes of life and partly improving on them, we shall learn to build self-reproducing machines programmed to multiply, differentiate, and coordinate their activities as skillfully as the cells of a higher organism such as a bird. After we have constructed a single egg machine and supplied it with the appropriate computer program, the egg and its progeny will grow into an industrial complex capable of performing economic tasks of arbitrary magnitude. It can build cities, plant gardens, construct electric power-generating facilities, launch space ships, or raise chickens. The overall programs and their execution will remain always under human control.*
>
> *The effects of such a powerful and versatile technology on human affairs are not easy to foresee. Used unwisely, it offers a rapid road to ecological disaster. Used wisely, it offers a rapid alleviation of all the purely economic difficulties of mankind. It offers to rich and poor nations alike a rate of growth of economic resources so rapid that economic constraints will no longer be dominant in determining how people are to live. In some sense this technology will constitute a permanent solution of man's economic problems. Just as in the past, when economic problems cease to be pressing, we shall find no lack of fresh problems to take their place.*

Self-replicating systems may be the key to low cost manufacturing but there is no need to allow such systems to function freely in the outside world. Restricted to an artificial and controlled environment, factory replicators can manufacture simpler and more rugged applications products which are then transferred to the end user. For example, medical devices designed to operate in the human body[228-236] or inside any other living thing should not self-replicate (see *Nanomedicine*,[228] Sections 1.3.3 and 2.4.2). Such devices can be manufactured in a controlled environment, then injected or implanted into the patient as required, and later removed when the job is done. The resulting medical devices will be simpler, smaller, more efficient and more precisely designed for the task at hand than devices designed to perform the same function *and* to self-replicate.[2928] Similar considerations apply to nonmedical applications of molecular nanotechnology.

Given the potential for accident and abuse[2,199,2909] (and see Section 6.3.1), artificial replicators will almost certainly be very tightly regulated by governments everywhere. For example, it is unlikely that the FDA (or its future or overseas equivalent) would ever approve for general use a nonbiological medical nanodevice that was capable of in vivo replication, evolution, or mutation. Guidelines to avoid accidents and foreseeable abuses have been promulgated for biotechnology replicators[2929] and have also been proposed for nanotechnology replicators.[271] There are many technical routes to ensuring "safe replication," most notably the broadcast architecture for control (Section 4.11.3.3) and the vitamin architecture for materials (Section 4.3.7) which eliminate almost any possibility that the system can replicate outside of a very controlled and highly artificial setting. Interestingly, the Heifer Project[2930] is an example of a safe self-replicating "technology" being philanthropically distributed to impoverished Third World countries to help combat world poverty and hunger.**

** Minsky does not recall making this exact claim[2922] and believes the original quotation came from a book written by Minsky in 1968,[2923] containing the following paragraph: "As one tries to classify all of one's knowledge, the categories grow rapidly at first, but after a while one encounters more and more difficulty. My impression, for what it is worth, is that one can find fewer than ten areas, each with more than ten thousand such links. Nor can one find a hundred things that one knows a thousand things about, or a thousand things, with a hundred such links. I therefore feel that a machine will quite critically need to acquire the order of a hundred thousand elements of knowledge in order to behave with reasonable sensibility in ordinary situations. A million, if properly organized, should be enough for a very great intelligence. If my argument does not convince you, multiply the figures by ten."*

From the more recent work done on large commonsense knowledge bases, Douglas Lenat's "CYC" Project and Push Singh's "OpenMind Commonsense" Project each have on the order of a million entries, and Minsky[2922] suspects "that each would need to be at least 10 times larger to 'know' as much as a not-very-well-informed person. So this suggests that a person might need between 10 and 100 millions of 'knowledge units' whatever these are." Positing that each 'element of knowledge' (with several 'links') would need on the order of a few hundred bits, Minsky[2922] estimates that "if we had to convert this to 'bits', that might come to the order of a few hundred megabytes. If this is right, then your mind might fit nicely onto a present day 700 MB CD-ROM. Another argument which favors this order of magnitude: psychologists have never found situations in which a person can store in long-term memory more than one or two 'items' per second. This suggests an upper bound of the order of 10 million units per year."

*** The problem of a runaway replicative factory system producing an uncontrolled overabundance, ostensibly for the benefit of human beings, was explored by Philip K. Dick in his 1955 story "Autofac":[668]*

Cut into the base of the mountains lay the vast metallic cube of the Kansas City factory. Its surface was corroded, pitted with radiation pox, cracked and scarred from the five years of war that had swept over it. Most of the factory was buried subsurface, only its entrance stages visible....

"The Institute of Applied Cybernetics had complete control over the network. Blame the war...we can't transmit our information to the factories — the news that the war is over and we're ready to resume control of industrial operations."

"And meanwhile," Morrison added sourly, "the damn network expands and consumes more of our natural resources all the time."

"Isn't there some limiting injunction?" Perine asked nervously. "Were they set up to expand indefinitely?"

"Each factory is limited to its own operational area," O'Neill said, "but the network itself is unbounded. It can go on scooping up our resources forever....It's already used up half a dozen basic minerals. Its search teams are out all the time, from every factory, looking everywhere for some last scrap to drag home....Each factory has its own special section of our planet, its own private cut of the pie for its exclusive use...They're raw material-tropic; as long as there's anything left, they'll hunt it down."

Fears that self-replicating machines or "machine life" could get out of control and even displace all biological life have been voiced by writers in the 1910s,[2931] 1920s,[657,658] 1930s,[660,2932] 1940s,[2933] 1950s,[663-668] 1960s,[669-673] 1970s,[2934-2938] 1980s,[2,199,2896] 1990s,[2910,2939] and 2000s,[2898-2909] though others are more hopeful.[2887,2940] Possible procedures and safeguards for the safe development of molecular-scale self-replicating systems were first discussed in Drexler's *Engines of Creation*,[199] and later by Forrest[2941] who listed a number of important regulatory issues and noted that "safe designs, safe procedures and methods to test for potentially hazardous assemblers can be incorporated into standards by consensus of interested parties." Regulation continued to be discussed within the membership of the Foresight Institute throughout the 1990s. These concepts were further developed in a workshop sponsored by Foresight Institute and the Institute for Molecular Manufacturing (IMM), and finally formalized in the "Foresight Guidelines on Molecular Nanotechnology" during 1999-2000. Neil Jacobstein of IMM conducted several open workshops on the Guidelines, and incorporated the resulting feedback into several subsequent draft versions. Both authors of this book (Freitas and Merkle) and many others participated[2942] in the drafting of the final Guidelines document.[271]

The core of the Guidelines[271] consists of three parts — first, a set of general principles; second, a set of development principles; and third, a set of specific design guidelines for molecular nanotechnology (MNT). These principles are crudely analogous to the original NIH Guidelines on Recombinant DNA technology[2929] in the field of biotechnology, an example of self-regulation first adopted by the biotechnology community almost three decades ago.

The Foresight **general principles** recommend that:

1. People who work in the MNT field should develop and utilize professional guidelines that are grounded in reliable technology, and knowledge of the environmental, security, ethical, and economic issues relevant to the development of MNT.
2. Access to the end products of MNT should be distinguished from access to the various forms of the underlying development technology. Access to MNT products should be unrestricted unless this access poses a risk to global security.
3. Accidental or willful misuse of MNT must be constrained by legal liability and, where appropriate, subject to criminal prosecution.
4. Governments, companies, and individuals who refuse or fail to follow responsible principles and guidelines for development and dissemination of MNT should, if possible, be placed at a competitive disadvantage with respect to access to MNT intellectual property, technology, and markets.
5. The global community of nations and non-governmental organizations need to develop effective means of restricting the misuse of MNT. Such means should not restrict the development of peaceful applications of the technology or defensive measures by responsible members of the international community.
6. MNT research and development should be conducted with due regard to existing principles of ecological and public health. MNT products should be promoted which incorporate systems for minimizing negative ecological and public health impact.
7. Any specific regulation adopted by researchers, industry or government should provide specific, clear guidelines. Regulators should have specific and clear mandates, providing efficient and fair methods for identifying different classes of hazards and for carrying out inspection and enforcement. There is great value in seeking the minimum necessary legal environment to ensure the safe and secure development of this technology.

The set of **development principles** includes:

1. Artificial replicators must not be capable of replication in a natural, uncontrolled environment.
2. Evolution within the context of a self-replicating manufacturing system is discouraged.
3. Any replicated information should be error free.
4. MNT device designs should specifically limit proliferation and provide traceability of any replicating systems.
5. Developers should attempt to consider systematically the environmental consequences of the technology, and to limit these consequences to intended effects. This requires significant research on environmental models, risk management, as well as the theory, mechanisms, and experimental designs for built-in safeguard systems.
6. Industry self-regulation should be designed in whenever possible. Economic incentives could be provided through discounts on insurance policies for MNT development organizations that certify Guidelines compliance. Willingness to provide self-regulation should be one condition for access to advanced forms of the technology.
7. Distribution of molecular manufacturing *development* capability should be restricted, whenever possible, to responsible actors that have agreed to use the Guidelines. No such restriction need apply to end products of the development process that satisfy the Guidelines.

The set of **specific design guidelines** includes:

1. Any self-replicating device which has sufficient onboard information to describe its own manufacture should encrypt it such that any replication error will randomize its blueprint.
2. Encrypted MNT device instruction sets should be utilized to discourage irresponsible proliferation and piracy.*
3. Mutation (autonomous and otherwise) outside of sealed laboratory conditions, should be discouraged.
4. Replication systems should generate audit trails.
5. MNT device designs should incorporate provisions for built-in safety mechanisms, such as: (a) absolute dependence on a single artificial fuel source or artificial "vitamins" that don't exist in any natural environment; (b) making devices that are dependent on broadcast transmissions for replication or in some cases operation; (c) routing control signal paths throughout a device, so that subassemblies do not function independently; (d) programming termination dates into devices; and (e) other innovations in laboratory or device safety technology developed specifically to address the potential dangers of MNT.
6. MNT developers should adopt systematic security measures to avoid unplanned distribution of their designs and technical capabilities.

In a June 2000 Foresight Institute press release,[2944] Zyvex Corp. became the first corporate supporter of the Guidelines principles. James Von Ehr, President and CEO of Zyvex, said: "This is an

---

** Freeman Dyson[2943] observes: "The idea which I found most interesting was the emphasis on encryption as a safeguard against hijacking. This raises a new question for biologists. All living creatures are fighting a constant battle against hijacking of their genetic and metabolic apparatus by viruses. Is there any evidence that cells have evolved encryption of vital genes and polymerase enzymes to stop viruses from taking over the apparatus? Could this be a reason for the subdivision of eukaryotic genes into exons and introns?"*

important document that deserves careful reading by all concerned. As one of the first nanotechnology companies, Zyvex fully supports the Guidelines and is pleased that two of our senior scientists [Merkle and Freitas] were able to participate in their preparation. I expect that a sense of professional ethics will compel nanotechnology developers to individually subscribe to these principles. These Guidelines are so important that grant-making agencies, even military ones, should require a pledge of adherence as a precondition of funding advanced nanotechnology development." The Foresight Guidelines appear to be considerably more restrictive than, for example, the "Bioethics Statement of Principles"[2945] to which companies at the forefront of engineered biological replicator development, such as Egea Biosciences,[2946] subscribe. Indeed, Freeman Dyson[2943] believes that the Guidelines may be "a bit too cautious. But they can always be relaxed later as experience accumulates, just as the recombinant DNA guidelines were relaxed."

During 2000-2003, Neil Jacobstein moderated several seminars at the Aspen Institute[2947] that incorporated the Foresight Guidelines as part of a larger dialog on "Opportunity, Risk and Responsibility" regarding nanotechnology. These seminars, as well as other workshops and presentations, served to expose the Guidelines to an increasingly larger community, and to lay the foundation for potential future revisions.

In April 2003, the Foresight President (Christine Peterson)[2948] and a Zyvex Board Member (Ray Kurzweil)[2949] were invited to testify before the U.S. House Science Committee, and later to advise on the wording of amendments to the "societal and ethical" part of the House Bill. The Foresight Guidelines were subsequently employed in producing the wording of an amendment to the Bill. H.R. 766, the National Nanotechnology Research and Development Act of 2003,[2950] which passed the House by an overwhelming majority on 7 May 2003 and was passed in similar form by the Senate on 22 June 2003.[2951] H.R. 766 Section 8(c) specifically calls for "A Study On Safe Nanotechnology" by the National Academy of Sciences and required, in the original* House language:

> *Not later than 6 years after the date of enactment of this Act a review shall be conducted in accordance with subsection (a) that includes a study to assess the need for standards, guidelines, or strategies for ensuring the development of safe nanotechnology, including those applicable to — (1) self-replicating nanoscale machines or devices; (2) the release of such machines or devices in natural environments; (3) distribution of molecular manufacturing development; (4) encryption; (5) the development of defensive technologies; (6) the use of nanotechnology as human brain extenders; and (7) the use of nanotechnology in developing artificial intelligence.*

The issue of public safety in connection with possible future nanotechnology-based replicators, though still downplayed in the European Community,[3114] has already begun to attract National Science Foundation (NSF) funding in the United States. The March 2001 NSF report,[2962] *Societal Implications of Nanoscience and Nanotechnology,* "produced a template for discussion but left particular investigations for the future."[2963] Soon thereafter, the University of South Carolina (USC) began "the first university-based interdisciplinary initiative to bring close scrutiny to this new area of science and technology," a series of studies which first received NSF funding in 2002[2963] and is planned to run through 2003-2007. These studies will specifically examine, among other related topics, the "problems of self-replication, risk, and cascading effects in nanotechnology." In August 2003, the NSF announced[2954] an award of $1.3 million[2955] funding for this effort.

According to the USC proposal,[2963] the Task Area 3 group will consider the management of risk in three clusters of investigation:

1. *Models of Self-Replication and Self-Regulation.* The researchers will "articulate the range of meanings encompassed by self-replication and self-regulation, from a simpler, bench-oriented model to the vision associated with assemblers, and everything in between. Nanoscientists have already developed a variety of new materials that show promise for nano-engineered products — nanotubes, electrically conducting compounds, quantum dots, etc. Now, they need ways to organize these materials into larger structures that might be useful to society. In order to do this, they have focused upon mechanisms of replication and the regulation of these mechanisms. But, as the complexity of a self-replicating process increases, the possibility of an undesirable medical or environmental outcome seems likely to increase as well, and there are additional concerns about potential mutations of the original process. In order to help anticipate and prepare for such possibilities, Task Area 3 team members will seek to identify the multiple models and meanings of self-replication and self-regulation, ranging from current techniques (e.g., for growing nanotubes) to universal assemblers. In between, we consider possibilities on the near horizon (e.g., the use of viruses to engineer at the nanoscale) and the more distant horizon (e.g., limited assemblers, the stated goal of the company Zyvex[2956])."

   "Task Area 3 members will approach this work by drawing on analogies between these engineered mechanisms and those found in natural biological systems. In order to appreciate the challenges involved in designing and manufacturing nano-structures capable of self-replication and correction without loss of control, they will examine the properties of natural self-replicating systems. What methods does nature use for self-replication? Will nanotechnologies resemble genetic systems in such a way that an understanding of the natural principles governing the latter might guide the development and application of the former in safe and controllable ways? In what ways will they differ? Armed with this understanding we will be able to explore the philosophical and ethical implications of aspects of self-regulation." The target publication date for this phase of the USC work is Spring 2005, and an edited volume on these issues will follow the Summer 2004 Workshop and the Spring 2005 Conference — both on these topics — in Fall 2006.

2. *Taxonomy of Risk Assessments for Nanotechnology.* "Scientists know that complex, non-linear, self-replicating systems can produce unanticipated medical and/or environmental harm. In some cases statisticians can quantify risks associated with such systems, but in many other cases the uncertainty is too great, and the best that can be done is to provide a less precise qualitative analysis.[2957] Along these lines, Task Area 3 team members will develop a taxonomy of the kinds of risk assessment that could be used in ethical debates on nanotechnology. First, they will identify risk paradigms for possible medical

---

** Unfortunately, the final language of the bill that was signed into law calls only for a study on "molecular self-assembly," or more specifically: "Section 5(b) Study on Molecular Self-Assembly — The National Research Council shall conduct a one-time study to determine the technical feasibility of molecular self-assembly for the manufacture of materials and devices at the molecular scale."[2952] Observes Glenn Reynolds:[2953] "Given that self-assembling nanodevices have already been demonstrated, taking a narrow view of this language seems unlikely to accomplish much. It's like performing a study to determine the feasibility of integrated circuit chips. Been there, done that. Presumably, the broader interpretation of the language will obtain. If it doesn't, that may be an early sign that federal officials aren't really serious about developing what most people would consider to be true molecular manufacturing. Let's hope it doesn't."*

and environmental outcomes (e.g., the way a new virus can pose a public health risk). Then they will consider whether the associated risks could have been anticipated and quantified in a risk analysis. They will examine cases where established methods of quantifying risk worked well and cases where the outcomes could not have been anticipated and quantified. Next they will draw on their earlier work, developing the analogy between engineered and natural nanosystems, and they will extend this analysis to consider the possibilities of quantifying risks associated with the types of self-replicating, artificially engineered nanosystems identified earlier. The goal is to identify and structure the variety of cases posed by nanotechnology in terms of the degree to which the risks can or cannot be quantified. Finally, within this structure they will consider how such risks can and should be incorporated into ethical analysis and communicated to the public."[2958] The target publication date for this phase is Spring 2006.

3. *The Literature and Culture Informing Ethical Analysis of Nanotechnology*. "There are several new areas of research that involve significant challenges to our understanding of ourselves and our prospects in the world. These include (i) robotics/cybernetics, (ii) genetics, and (iii) nanotechnology. In most of this literature, these three technologies are considered in isolation. However, some of the most troubling ethical issues occur where all three technologies intersect. Task Area 3 members will explore analogies, similarities, and differences between the ethical discussions in each of these areas and then consider how their combination could raise issues that have been insufficiently considered when viewed in isolation. The focus here will not only be on the substance of the issues, but also on the climate and culture that frames the way the issues are addressed and resolved." The target publication date for this phase of the USC work is Spring 2007.

The study of the ethical,[2959] socioeconomic[2,2960-2963] and legal[2964-2967] impact of machine replicators is still in its earliest stages, and additional discussion of safety issues may be found in Sections 2.1.5, 2.3.6, 5.1.9(L), 6.3.1 and 6.4.4. However, two important general observations about replicators and self-replication should be noted here.

First, **replication is nothing new**. Humanity has thousands, arguably even millions, of years of experience living with entities that are capable of kinematic self-replication. These replicators range from the macroscale (e.g., insects, birds, horses, other humans) on down to the microscale (e.g., bacteria, protozoa) and even the nanoscale (e.g., prions, viruses). As a species, we have successfully managed the eternal tradeoff between risk and reward, and have successfully negotiated the antipodes of danger and progress. There is every reason to expect this success to continue.

The technology of engineered self-replication, even at the microscale, is already in wide commercial use throughout the world. Indeed, human civilization is utterly dependent on self-replication technologies. Many important foods including beer, wine, cheese, yogurt, and kefir (a fermented milk), along with various flavors, nutrients, vitamins and other food ingredients, are produced by specially cultured microscopic replicators such as algae, fungi (yeasts) and bacteria. Virtually all of the rest of our food is made by macroscale replicators such as agricultural crop plants, trees, and farm animals. Many of our most important drugs are produced using microscopic self-replicators — from penicillin produced by natural replicating molds starting in the 1940s[228] to the first use of artificial (engineered) self-replicating bacteria to manufacture human insulin by Eli Lilly in 1982.[2968] These uses continue today in the manufacture of many other drug products such as: (a) human growth hormone (HGH) and erythropoietin (EPO), (b) precursors for antibiotics such as erythromycin,[2969] and (c) therapeutic proteins such as Factor VIII. A few species of self-replicating bacteria are used directly as therapeutic medicines, such as the widely available swallowable pills containing bacteria (i.e., natural biological nanomachines) for gastrointestinal refloration, as for example Salivarex™ which "contains a minimum of 2.9 billion beneficial bacteria per capsule",[2970] and Alkadophilus™ which "contains 1.5 billion organisms per capsule",[2971] both at a 2003 price of $\sim\$(0.1\text{-}0.2) \text{ x } 10^{-9}$ per microscale replicator (i.e., per bacterium). Some replicating viruses, notably bacteriophages, are used as therapeutic agents to combat and destroy unhealthful infectious bacterial replicators,[1757] and for decades viruses have served as transfer vectors to attempt gene therapies.[2972-2975] In industry, bacteria are already employed as "self-replicating factories"[1779-1781] for various useful products, and microorganisms are also used as workhorses for environmental bioremediation*,[2976-2979] biomining of heavy metals,[2980-2983] and other applications. In due course we will learn to safely harness the abilities of nonbiological kinematic machine replicators for human benefit as well.

Second, **replicators can be made inherently safe**. An "inherently safe" kinematic replicator is a replicating system which, by its very design, is inherently incapable of surviving mutation or of undergoing evolution (and thus evolving out of our control or developing an independent agenda), and which, equally importantly, does not compete with biology for resources (or worse, use biology *as* a raw materials resource).[2909] One primary route for ensuring inherent safety is to employ the broadcast architecture for control (Section 4.11.3.3) and the vitamin architecture for materials (Section 4.3.7), which eliminate the likelihood that the system can replicate outside of a very controlled and highly artificial setting, and there are numerous other routes to this end (Section 5.1.9 and see Guidelines, above). Many dozens of additional safeguards may be incorporated into replicator designs to provide redundant embedded controls and thus an arbitrarily low probability of replicator malfunctions of various kinds, simply by selecting the appropriate design parameters as described in Section 5.1.9.

Artificial kinematic self-replicating systems which are not inherently safe should not be designed or constructed, and indeed should be legally prohibited by appropriate juridical and economic sanctions, with these sanctions to be enforced in both national and international regimes. In the case of individual lawbreakers or rogue states that might build and deploy unsafe artificial mechanical replicators, the defenses we have already developed against harmful biological replicators all have analogs in the mechanical world that should provide equally effective, or even superior, defenses. Molecular nanotechnology will make possible ever more sophisticated methods of environmental monitoring and prophylaxis. However, advance planning and strategic foresight will be essential in maintaining this advantage. (See also Section 6.3.1.)

** According to Press:[2979] "The first patented form of life produced by genetic engineering was a greatly enhanced oil-eating microbe. The patent[2984,2985] was registered to Dr. Ananda Chakrabarty of the General Electric Company in 1981 and was initially welcomed as an answer to the world's petroleum pollution problem. But anxieties about releasing 'mutant bacteria' soon led the U.S. Congress and the Environmental Protection Agency (EPA) to prohibit the use of genetically engineered microbes outside of sealed laboratories. The prohibition set back bioremediation for a few years, until scientists developed improved forms of oil-eating bacteria without using genetic engineering. After large-scale field tests in 1988, the EPA reported that bioremediation eliminated both soil and water-borne oil contamination at about one-fifth the cost of previous methods. Since then, bioremediation has been increasingly used to clean up oil pollution on government sites across the United States."*

CHAPTER 6

Motivations for Molecular-Scale Machine Replicator Design

In 1959, Feynman[2182] proposed that we could arrange atoms in most of the ways permitted by physical law. Von Neumann[3] analyzed a few basic architectures for self-replicating systems in the 1940s and early 1950s, and several possible implementations of von Neumann's kinematic replicators were described by Freitas and Gilbreath[2] in the context of macroscale space-based manufacturing systems during a NASA study in 1980 (Section 3.13). In the early 1980s, Drexler[197,199] proposed the molecular assembler — a nanoscale device able to rearrange atoms and to self-replicate — and subsequently analyzed the fundamental technical issues involved.[208] Following these and other early efforts in replication theory,[200,201] the feasibility of building an artificial replicator and of molecular manufacturing has gradually come to be accepted although some still claim that artificial programmable self-replicating manufacturing systems that differ fundamentally from biological designs are impossible.[13,14,3000] These and other claims of impossibility[15,202-206,2310] are poorly supported.[16,17,207] After many decades of discussion and debate, no valid technical arguments against the feasibility of artificial replicators generally, or against the feasibility of molecular assemblers in particular, are known to the authors. By contrast, there are many proposals and analyses that support the feasibility of such systems.

While the absence of valid technical counterarguments is reassuring, existing design proposals have not been carried out in sufficient detail to permit construction, even if appropriate molecular tools were available. If we are to develop assemblers, a necessary first step is to fully specify at least some of the simpler members of this genre. The result of a successful molecular assembler design effort would include at least one specific comprehensive design (given, for example, as a series of atomic coordinates and chemical elements specifying the position and type of every atom in the assembler) and accompanying analyses showing the validity of the design with respect to various criteria — e.g., that the proposed structures are stable at the intended operating temperature, the positional devices are sufficiently stiff to provide accurate positioning of the molecular tools at the intended operating temperature, the reactions mediated by the molecular tools would work correctly,[1] the structures/parts described in the design can be synthesized both by a proto-assembler and by the designed assembler itself, and so forth.

6.1 Initial Motivations for Study

Although the design of a molecular assembler has been feasible for many years and basic design issues have been addressed by Drexler,[197-199,208] Merkle,[209-221] and several others,[219-225,228,2322-2325] surprisingly little organized effort has been devoted to it. There exists, at the present time, no national program to design an assembler and no related university or academic projects, despite calls over the years for just such a national level effort equivalent in magnitude to the Manhattan Project or the Apollo Moon Program. For example, in 1992 Neil Jacobstein observed:[3001]

> *Revolutions in science and engineering all start from a set of insights on technical feasibility and payoffs. However, nothing much happens until people with access to resources commit to making something happen. Envisioning a fundamental advance in technology requires deep knowledge and insight, but making it happen requires access to vast resources, and systematic hard work sustained over a long period of time.... The goal, I believe, should be nothing less than a peacetime Manhattan Project — an international collaboration of industry and government to really accomplish molecular manufacturing.*

In the private sector, only a single company (Zyvex[2956]) has explicitly pursued molecular assembler design as a long-term objective. Even acknowledging that the time required to build the first prototypes is likely to be long, this state of affairs can only be described as astonishing. The potential payoff,[199,226-228] as measured by almost any rational metric, is so enormous that it would seem to justify an effort representing some non-negligible fractional percentage of the nation's GDP (Gross Domestic Product) — especially since other organizations or countries might have more advanced, or better-targeted, programs to develop molecular nanotechnology and molecular assemblers. Molecular manufacturing may be the ultimate "disruptive technology".[3002]

In this Chapter we review both the arguments favoring a focused design effort and the arguments opposing such an effort, then identify specific goals for a well-focused future design effort.

6.2 Arguments Favoring a Focused Design Effort

Arguments favoring a focused design effort include the proposition that design precedes construction (Section 6.2.1), the need for a demonstration of feasibility (Section 6.2.2), and the need to clarify the proposal (Section 6.2.3).

6.2.1 Design Precedes Construction

First and foremost, it seems unlikely that we can build an assembler in the absence of a design. It is difficult to know how long it might take to develop an assembler (including not only design but construction of early prototypes), but estimates are generally measured in decades. While the authors believe that one to two decades is plausible, and while most estimates range from one to four decades, a minority of knowledgeable observers claim that it will take longer.

Whatever the development time, it should be possible to shorten it significantly by the widespread availability in the technical community of one or more feasible designs. These designs would permit a more careful analysis of the capabilities required for construction, and would therefore focus attention on those experimental approaches that could most effectively speed development. A design believed to be correct, but as yet unbuildable using present-day manufacturing techniques, can enable further design efforts in which the minimal design is backchained toward currently accessible manufacturing techniques such as scanning probe microscopy.[3003] As Merkle[212] noted in a related context: "The direct manufacture of this 'simple' system with current technology seems unlikely to be feasible. As a consequence, it will probably be necessary to develop other systems that are easier to synthesize using today's methods, but which are sufficiently powerful that we can use them to synthesize more sophisticated systems. This might be likened to the ascent of a tall mountain in stages, with base camps established at intermediate elevations. The precise nature of these intermediate stages depends on the design of the final stage. The present proposal might be likened to a final base camp, close enough to the peak that it's clear that a final assault from this final base camp would reach the peak, but far enough removed that it's significantly easier to reach the base camp than the peak." It is useful, of course, to recall that just as in mountain climbing, one should not confuse mere glimpses of the summit with proximity to that goal.

As Drexler[208] explained in 1992: "In a *forward chaining* search (as the term is used in computer science), one pursues a goal by taking steps that may lead toward it, sometimes exploring blind alleys. If, however, all possible destinations are considered equally good, then there is no real goal, hence (by this loose standard) forward chaining never fails. In science, it is common to pursue experimental programs opportunistically, choosing next steps based on immediate prospects and a sense of what is interesting, important, and fundable. This process resembles forward chaining with abundant, unranked goals, and it routinely produces incremental advances in knowledge and capabilities.

"In *backward chaining*, one first describes a goal, then searches for intermediate situations one step removed from the goal, then for situations one step removed from *those*, and so forth, planning backward toward situations that are immediately accessible — that is, toward potential first steps on an implementation pathway. If there are many potential first steps, then backward chaining can be particularly attractive. In technology, it is common to select a goal based on its near-term feasibility and economic attractiveness and then plan backward to select the necessary parts and procedures. The enormous range of modern technological capabilities often provides many possibilities, hence engineers are more often concerned with cost and performance than with feasibility alone.

"Molecular manufacturing is a technological goal (representing many scientific challenges), but it cannot be achieved in a few steps or a few years. Accordingly, one cannot expect to succeed by combining just existing parts and procedures. Backward chaining is still appropriate, but the links in the chain are intermediate technologies, not mere parts and assembly procedures."

It is likely that the existence of one well-developed proposal, with its specific parameters and results, would inspire efforts to produce competitive proposals (whether related or diverse) that are improvements in some way. This intellectual competition would contribute to further useful explorations of the design space.

6.2.2 Demonstration of Feasibility

A second reason motivating a molecular assembler design project is to show feasibility. At the present time, not all members of the research community (and as a consequence not all decisionmakers) will agree that assemblers are possible. Molecular models of critical components and subsystems will provide both a more detailed technical analysis of the issues and also a basis for graphics, animations, and other visual aids that can vividly and compellingly communicate the salient issues. Clearly, devoting substantial resources to a project is made more difficult if there is significant doubt about its ultimate feasibility. A detailed design effort should lay such doubts to rest, at least within the most crucial scientific and engineering communities that closely follow research in this area.

Further, one or more credible published designs demonstrating feasibility should increase the absolute magnitude of the resources devoted to the development of a molecular assembler. A feasible design would drive home the point that assemblers are possible, a fact that would influence funding sources to direct additional resources towards their development. For instance, an issue of significant interest is the use of self replication to reduce manufacturing costs. Self replication is likely to have a revolutionary impact on the economics of manufacturing, driving the manufacturing cost per pound for most manufactured products down to levels seen in existing products made using a self-replicating manufacturing base, such as agricultural products (wood, wheat, etc.) or even lower. As an example, consider the impact of a one kilogram molecular memory with a storage capacity measured in moles of bits (a mole is ~6 x 10^{23}, a unit of quantity common in chemistry) and an eventual total manufacturing cost, at least in principle, as low as $1-$1000 per kilogram, comparable to the prices of various products made by present-day biology-based self-replicating manufacturing systems (Table 6.1). The basic cost of production using a mature molecular manufacturing technology base, excluding development, distribution and legally-mandated costs, will be dominated by the price of materials (*Nanosystems*[208] at Section 14.5.6.h), which presently cost ~0.1-0.5 $/kg (e.g., propane for manufacturing diamond; Table 6.1). This alone would revolutionize computer hardware capabilities. Yet this is but a single example of the numerous consequences of molecular manufacturing — a manufacturing technology which will transform most other manufactured products equally profoundly.

A cautionary historical analogy can be mentioned in connection with the development of the scanning tunneling microscope (STM) which is now employed for direct atomic visualization and other useful purposes in molecular nanotechnology. While it is well known that Gerd Karl Binnig and Heinrich Rohrer received the Nobel Prize for inventing the STM in 1981 at an IBM laboratory in Zurich, Switzerland,[3021] what is perhaps less well known is that the first STM, complete with piezo scanning system, was almost invented a decade earlier.[3022] In 1971, Young, Ward and Scire reported metal-vacuum-metal tunneling experiments[3023] and described a machine they had built[3024] for these experiments at the National Bureau of Standards: "A noncontacting instrument for measuring the microtopography of metallic surfaces has been developed to the point where the feasibility of constructing a prototype instrument has been demonstrated.... In the MVM [metal-vacuum-metal] mode, the instrument is capable of performing a non-contacting measurement of the position of a surface to within about 3 Angstroms. The

Table 6.1. Current bulk prices of nanoscale-structured products manufactured in macroscale quantities by present-day biology-based self-replicating manufacturing systems

Product Manufactured by the Replicator	Replicator	Price per Unit Mass
Firewood (note 1)	oak tree	$ 0.07/kg
Propane (note 2)	extinct species	$ 0.31/kg
Cotton (note 3)	cotton plant	$ 0.86/kg
Wool (note 4)	sheep	$ 0.99/kg
Eggs (note 5)	chickens	$ 1.46/kg
Beef (note 6)	cattle	$ 1.74/kg
Mulberries (note 7)	trees	$ 22.00/kg
Silk (note 8)	silkworms	$ 22.94/kg
Filet mignon steak (note 9)	cattle	$ 88.00/kg
Gastrointestinal microflora (note 10)	bacteria	$ 400.00/kg
Beluga caviar (note 11)	fish	$ 796.46/kg
Pearls (note 12)	oysters	$ 27,165.00/kg
HeLa cells (note 13)	cancer cells	$ 216,000.00/kg
Interferon (note 14)	biology	$ 190,000,000.00/kg
Other manufacturing prices for comparison:		
Typical residential house (note 15)	humans	$ 1.00/kg
Luxury automobile (note 16)	humans	$ 36.78/kg
1.4 GHz laptop computer (note 17)	humans	$ 824.00/kg
Gold coins (note 18)	humans	$ 12,900.00/kg
Unpurified carbon SWNTs (note 19)	humans	$ 50,000.00/kg
Purified carbon SWNTs (note 20)	humans	$ 500,000.00/kg
Microprocessor active surface (note 21)	humans	$ 6,880,000.00/kg
Cut diamonds (note 22)	humans	$ 28,000,000.00/kg

Notes:

1. oak firewood at $200/cord (typical 2003 price in Northern California), taking 128 ft^3/cord, 50 lbs/ft^3, and 0.4536 kg/lb.
2. U.S. average wholesale propane price in December 2003: $ 0.696/gallon[3004]
3. U.S. wholesale price of cotton in 2000: $0.3911/lb[3005]
4. U.S. wholesale price of wool in 2000: $0.45/lb[3005]
5. combined regional price, extra large shell eggs, in 2004[3006] is $1.0946/dozen eggs; mass of one extra large egg is ~2.2 oz, or 0.06237 kg/egg.
6. beef heifers, weighted price all grades, 2004: $79.02/100 lbs[3007]
7. fresh mulberries, U.S. price, 2000: $10-$15/lb[3008]
8. raw silk from silkworms, Chinese export price, 2001: 5688 metric tons of exports valued at $130.48 million[3009]
9. beef filet mignon at fancy French restaurant, assuming $25 for a 10 oz steak.
10. Alkadophilus™ gastrointestinal therapeutic refloration bacteria, 2004: $0.20/pill for ~0.5 cm^3 pills[2971]
11. Beluga caviar, Russian importer, 2004: $90 per 113 gm container[3010]
12. cultured Akoya pearls, Chinese exporter, 2004: one strand of 53 AA quality pearls for $1250;[3011] pearls are 8.5 mm diameter with mean density ~2.7 gm/cm^3,[3012] giving 0.868 gm per pearl.
13. HeLa cancer cell line, 1998: $216 per 1 cm^3 ampule[3013]
14. treatments for multiple sclerosis using two closely related ~22.5 kilodalton interferons administered in dosages of ~1 milligram/week at a treatment cost of ~$10,000/yr in 1996.[3014]
15. single-story 2000 square foot house, concrete slab, wood frame, assuming 100 metric ton total mass and $100,000 purchase price in 2004.
16. 2003 Lexus SC 430 2-door convertible, shipping weight 3,730 lbs, retail purchase price $62,225 on 28 January 2004.[3015]
17. 1.4 GHz Dell Inspiron 8600 laptop computer with all upgrades, 6.9 lbs with purchase price of $2579 in 2004.[3016]
18. gold, current market price at of January 2004: $400/troy oz
19. unpurified carbon single-walled nanotubes (SWNTs): $50/gram quoted by MER Corp. and Carbon Solutions[3017]
20. purified carbon single-walled nanotubes (SWNTs): $500/gram quoted by CNI[3018]
21. microprocessor chip with 10 micron thick active layer;[3019] Pentium 4 chip occupies an area of 131 mm^2 on a wafer,[3020] with an estimated manufacturing cost of $21/chip;[3020] 2.33 gm/cm^3 density of Si and SiO_2 assumed for microchip active layer of volume 1.31×10^{-9} m^3 per microchip.
22. Gemstone diamond (natural), investment grade D flawless, cut gemstones, 1-carat size, 1997 JCK market quotes: $28,000/gm

instrument can be used in certain scientific experiments to study the density of single and multiple atom steps on single crystal surfaces, absorption of gases, and processes involving electronic excitations at the surfaces." Although close to constructing a complete STM, this early effort was frustrated when the researchers' funding was suddenly cut in 1972, just as their work was about to bear fruit.[3022]

It is possible that potential funding sources have not yet internalized the magnitude of the benefits that can reasonably be expected from the development of molecular nanotechnology. A design illustrating basic feasibility should help some decisionmakers grasp the importance of the remarkable opportunities which confront us, and provide greater incentive to allocate resources to the entire research and development enterprise. In a 2003 public debate[3000] with Richard Smalley, Eric Drexler observed that "U.S. progress in molecular manufacturing has been impeded by the dangerous illusion that it is infeasible. However, because it is a systems engineering goal, molecular manufacturing cannot be achieved by a collection of uncoordinated science projects. Like any major engineering goal, it will require the design and analysis of desired systems, and a coordinated effort to develop parts that work together as an integrated whole. Why does this goal matter? Elementary physical principles indicate that molecular manufacturing will be enormously productive. Scaling down moving parts by a factor of a million multiplies their frequency of operation — and in a factory, their productivity per unit mass — by the same factor. Building with atomic precision will dramatically extend the range of potential products, and decrease environmental impact as well. The resulting abilities will be so powerful that, in a competitive world, failure to develop molecular manufacturing would be equivalent to unilateral disarmament."

On the other hand, the benefits may appear to other decisionmakers as "too good to be true," a phenomenon David Berube calls "nanohype".[3025] Cautions Drexler:[3026] "The very breadth of this range of applications has stimulated a reflexive rejection of the possibility of the enabling technology. This is, however, like rejecting data on the neutron-induced fission cross-section of the U-235 nucleus in 1940 because one disbelieves the possibility of a million-fold increase in the energy density of explosive devices. The magnitude of the expected consequences gives reason for careful evaluation of feasibility, not for emotional dismissals. Thus far, the dismissals have effectively inhibited the feasibility studies." Berube[3025] also observes that "venture capital sources have drained out due to the overuse of the nano prefix which seems to be attached to advanced MEMS research companies all over this country and abroad."

6.2.3 *Clarifying the Proposal*

A third powerful motivation for studying molecular assembler design is the need to clarify the proposal. At the present time, many research scientists support the general claim that we should eventually be able to arrange atoms in most of the ways permitted by physical law, and that artificial programmable self-replicating systems are feasible. However, many of those researchers who are supportive of these general claims do not as yet have a clear and specific understanding of what a system able to arrange atoms and to self-replicate might look like. The only existing system designs that are widely understood are biological in character — and biological systems are notably deficient in several critical areas from the perspective of manufacturing.

An important motivation of this book, as well as future studies, is to help eliminate certain popular misconceptions about replicators and the process of self-replication. The term "self replication" carries assumptions and connotations (mostly derived from biological systems) that are grossly incorrect or misleading when applied to many proposed machine self-replicating systems. For example, some people assume that replicating systems must (a) be like living systems, (b) be adaptable (able to survive in the natural environment), (c) be very complex, (d) have onboard instructions, (e) be self-sufficient (using only very simple or basic parts), (f) be able to evolve into systems more powerful than us, and (g) come to view all living things, including us, as their food. As demonstrated elsewhere in this book, none of these assumptions is correct.

Such misconceptions are more than of mere academic interest and could actually prove quite harmful. That's because the fear of self-replicating systems[2908] is often based on misconceptions related to safety or assumptions about the supposed absence of viable control schemes. These misplaced fears could block needed research and thus prevent the acquisition of a deeper understanding of certain kinds of highly specialized systems that might pose serious concerns.[271] This is particularly true when programs and researchers avoid molecular assembler R&D for reasons of political convenience.

6.3 Arguments Against a Focused Design Effort

Arguments opposing a focused design effort include the propositions that molecular assemblers are too dangerous (Section 6.3.1), are impossible (Section 6.3.2), or have not yet been demonstrated (Section 6.3.3), that early design will not speed development (Section 6.3.4), that assemblers would be no better than conventional alternatives (Section 6.3.5), that potential design errors would make the analysis inherently worthless (Section 6.3.6), that macroscale-inspired machinery won't work at the nanoscale (Section 6.3.7), and that the design is too obvious (Section 6.3.8). We review these arguments here and find them to be unconvincing. Indeed, many of them are demonstrably unfounded.

6.3.1 *Molecular Assemblers Are Too Dangerous*

The first argument against a molecular assembler design effort is that the end results are too dangerous. According to this argument,[2905,2908] any research into molecular assemblers should be blocked because this technology might be used to build systems that could cause extraordinary damage. The kinds of concerns that nanoweapons systems might create have been discussed elsewhere, in both the nonfictional[2909,3027-3030,3113] and fictional[2898,3031,3032] literature. Perhaps the earliest-recognized and best-known danger of molecular nanotechnology is the risk that self-replicating nanorobots capable of functioning autonomously in the natural environment could quickly convert that natural environment (e.g., "biomass") into replicas of themselves (e.g., "nanomass") on a global basis, a scenario usually referred to as the "gray goo problem" but more accurately termed "global ecophagy".[2909] As Drexler first warned in *Engines of Creation* in 1986:[199]

> *"Plants" with "leaves" no more efficient than today's solar cells could out-compete real plants, crowding the biosphere with an inedible foliage. Tough omnivorous "bacteria" could out-compete real bacteria: They could spread like blowing pollen, replicate swiftly, and reduce the biosphere to dust in a matter of days. Dangerous replicators could easily be too tough, small, and rapidly spreading to stop — at least if we make no preparation.... We cannot afford certain kinds of accidents with replicating assemblers.*

Such self-replicating systems, if not countered, could make the earth largely uninhabitable[199,666,695,2898,2909] — concerns that motivated the drafting of the Foresight Guidelines for the safe development of nanotechnology[271] (Section 5.11). But as the Center for Responsible Nanotechnology explains:[3029]

> *Gray goo would entail five capabilities integrated into one small package. These capabilities are:* ***Mobility*** *— the ability to travel through the environment;* ***Shell*** *— a thin but effective barrier to keep out diverse chemicals and ultraviolet light;* ***Control*** *— a complete set of blueprints and the computers to interpret them (even working at the nanoscale, this will take significant space);* ***Metabolism*** *— breaking down random chemicals into simple feedstock; and* ***Fabrication*** *— turning feedstock into nanosystems. A nanofactory would use tiny fabricators, but these would be inert if removed or unplugged from the factory. The rest of the listed requirements would require substantial engineering and integration.*[2909]
>
> *Although gray goo has essentially no military and no commercial value, and only limited terrorist value, it could be used as a tool for blackmail. Cleaning up a single gray goo outbreak would be quite expensive and might require severe physical disruption of the area of the outbreak (atmospheric and oceanic goos*[2909] *deserve special concern for this reason). Another possible source of gray goo release is irresponsible hobbyists. The challenge of creating and releasing a self-replicating entity apparently is*

> *irresistible to a certain personality type, as shown by the large number of computer viruses and worms in existence. We probably cannot tolerate a community of "script kiddies"* releasing many modified versions of goo.*
>
> *Development and use of molecular manufacturing poses absolutely no risk of creating gray goo by accident at any point. However, goo type systems do not appear to be ruled out by the laws of physics, and we cannot ignore the possibility that the five stated requirements could be combined deliberately at some point, in a device small enough that cleanup would be costly and difficult. Drexler's 1986 statement can therefore be updated: We cannot afford criminally irresponsible misuse of powerful technologies. Having lived with the threat of nuclear weapons for half a century, we already know that.*

Attempts to block or "relinquish"[2908,3035] molecular nanotechnology research will make the world a more, not less, dangerous place.[3036] This paradoxical conclusion is founded on two premises. First, attempts to block the research will fail. Second, such attempts will preferentially block or slow the development of defensive measures by responsible groups. One of the clear conclusions reached by Freitas[2909] was that effective countermeasures against self-replicating systems should be feasible, but will require significant effort to develop and deploy. (Nanotechnology critic Bill Joy, responding to Freitas, complained in late 2000 that any nanoshield defense to protect against global ecophagy "appears to be so outlandishly dangerous that I can't imagine we would attempt to deploy it."[3035]) But blocking the development of defensive systems would simply insure that offensive systems, once deployed, would achieve their intended objective in the absence of effective countermeasures. James Hughes[3036] concurs: "The only safe and feasible approach to the dangers of emerging technology is to build the social and scientific infrastructure to monitor, regulate and respond to their threats."

We can reasonably conclude that blocking the development of defensive systems would be an extraordinarily bad idea. Actively encouraging rapid development of defensive systems by responsible groups while simultaneously slowing or hindering development and deployment by less responsible groups ("nations of concern") would seem to be a more attractive strategy, and is supported by the Foresight Guidelines.[271] As even nanotechnology critic Bill Joy[3037] finally admitted in late 2003: "These technologies won't stop themselves, so we need to do whatever we can to give the good guys a head start."

While a 100% effective ban against development might theoretically be effective at avoiding the potential adverse consequences, blocking all groups for all time does not appear to be a feasible goal. The attempt would strip us of defenses against attack, increasing rather than decreasing the risks. In addition, blocking development would insure that the substantial economic, environmental, and medical benefits[228] of this new technology would not be available.

Observes Glenn Reynolds:[3038] "To the extent that such efforts [to ban all development] succeed, the cure may be worse than the disease. In 1875, Great Britain, then the world's sole superpower, was sufficiently concerned about the dangers of the new technology of high explosives that it passed an act barring all private experimentation in explosives and rocketry. The result was that German missiles bombarded London rather than the other way around. Similarly, efforts to control nanotechnology, biotechnology or artificial intelligence are more likely to drive research underground (often under covert government sponsorship, regardless of international agreement) than they are to prevent research entirely. The research would be conducted by unaccountable scientists, often in rogue regimes, and often under inadequate safety precautions. Meanwhile, legitimate research that might cure disease or solve important environmental problems would suffer."

Finally, and as previously explained (e.g., Sections 3.13.2.2, 4.9.3, 4.14, 4.17, 4.19, 5.7, and 5.9.4), it is well-known[208] that self-replication activities, as distinct from the inherent *capacity* for self-replication, are not strictly required to achieve the anticipated broad benefits of molecular manufacturing. By restricting the capabilities of nanomanufacturing systems simultaneously along multiple design dimensions (Section 5.1.9) such as control autonomy (A1), nutrition (E4), mobility (E10) and immutability (L3, L4), molecular manufacturing systems — whether microscale or macroscale — can be made inherently safe. As Drexler[3106] noted in a 2004 paper:

> *In 1959, Richard Feynman pointed out that nanometer-scale machines could be built and operated, and that the precision inherent in molecular construction would make it easy to build multiple identical copies. This raised the possibility of exponential manufacturing, in which production systems could rapidly and cheaply increase their productive capacity, which in turn suggested the possibility of destructive runaway self-replication. Early proposals for artificial nanomachinery focused on small self-replicating machines, discussing their potential productivity and their potential destructiveness if abused.... [But] nanotechnology-based fabrication can be thoroughly non-biological and inherently safe: such systems need have no ability to move about, use natural resources, or undergo incremental mutation. Moreover, self-replication is unnecessary: the development and use of highly productive systems of nanomachinery (nanofactories) need not involve the construction of autonomous self-replicating nanomachines.... Although advanced nanotechnologies could (with great difficulty and little incentive) be used to build such devices, other concerns present greater problems. Since weapon systems will be both easier to build and more likely to draw investment, the potential for dangerous systems is best considered in the context of military competition and arms control.*

Of course, it must be conceded that while nanotechnology-based manufacturing systems can be made safe, they could also be made dangerous. Just because free-range self-replicators may be "undesirable, inefficient and unnecessary"[3106] does not imply that they

---

** According to cyberjournalist Clive Thompson,[3034] elite writers of software viruses openly publish their code on Web sites, often with detailed descriptions of how the program works, but don't actually release them. The people who do release the viruses are often anonymous mischief-makers, or "script kiddies" — a derisive term for aspiring young hackers, "usually teenagers or curious college students, who don't yet have the skill to program computers but like to pretend they do. They download the viruses, claim to have written them themselves and then set them free in an attempt to assume the role of a fearsome digital menace. Script kiddies often have only a dim idea of how the code works and little concern for how a digital plague can rage out of control. Our modern virus epidemic is thus born of a symbiotic relationship between the people smart enough to write a virus and the people dumb enough — or malicious enough — to spread it."*

Thompson goes on to describe his early 2004 visit to an Austrian programmer named Mario, who cheerfully announced that in 2003 he had created, and placed online at his website, freely available, a program called "Batch Trojan Generator" that autogenerates malicious viruses. Thompson described a demonstration of this program: "A little box appears on his laptop screen, politely asking me to name my Trojan. I call it the 'Clive' virus. Then it asks me what I'd like the virus to do. Shall the Trojan Horse format drive C:? Yes, I click. Shall the Trojan Horse overwrite every file? Yes. It asks me if I'd like to have the virus activate the next time the computer is restarted, and I say yes again. Then it's done. The generator spits out the virus onto Mario's hard drive, a tiny 3KB file. Mario's generator also displays a stern notice warning that spreading your creation is illegal. The generator, he says, is just for educational purposes, a way to help curious programmers learn how Trojans work. But of course I could ignore that advice."

Apparently top "malware' writers do take some responsible precautions, notes Thompson. For example, one hacker's "main virus-writing computer at home has no Internet connection at all; he has walled it off like an airlocked biological-weapons lab, so that nothing can escape, even by accident." Some writers, after finishing a new virus, "immediately e-mail a copy of it to antivirus companies so the companies can program their software to recognize and delete the virus should some script kiddie ever release it into the wild.

cannot be built, or that nobody will build them. How can we avoid "throwing out the baby with the bathwater"? The correct solution, first explicitly proposed by Freitas[2909] in 2000* and later partially echoed by Phoenix and Drexler[3106] in 2004,** starts with a carefully targeted moratorium or outright legal ban on the most dangerous kinds of nanomanufacturing systems, while still allowing the safe kinds of nanomanufacturing systems to be built — subject to appropriate monitoring and regulation commensurate with the lesser risk that they pose.

Virtually every known technology comes in "safe" and "dangerous" flavors which necessarily must receive different legal treatment. For example, over-the-counter drugs are the safest and most difficult to abuse, hence are lightly regulated; prescription drugs, more easy to abuse, are very heavily regulated; and other drugs, typically addictive narcotics and other recreational substances, are legally banned from use by anyone, even for medicinal purposes. Artificial chemicals can range from lightly regulated household substances such as Clorox or ammonia; to more heavily regulated compounds such as pesticides, solvents and acids; to the most dangerous chemicals such as chemical warfare agents which are banned outright by international treaties. Another example is pyrotechnics, which range from highway flares, which are safe enough to be purchased and used by anyone; to "safe and sane" fireworks, which are lightly regulated but still available to all; to moderately-regulated firecrackers and model rocketry; to minor explosives and skyrockets, which in most states can be legally obtained and used only by licensed professionals who are heavily regulated; to high-yield plastic explosives, which are legally accessible only to military specialists; to nuclear explosives, the possession of which is strictly limited to a handful of nations via international treaties, enforced by an international inspection agency. Yet another example is aeronautics technology, which ranges from safe unregulated kites and paper airplanes; to lightly regulated powered model airplanes operated by remote control; to moderately regulated civilian aircraft, both small and large; to heavily regulated military attack aircraft such as jet fighters and bombers, which can only be purchased by approved governments; to intercontinental ballistic missiles, the possession of which is strictly limited to a handful of nations via international treaties.

Note that in all cases, the existence of a "safe" version of a technology does not preclude the existence of a "dangerous" version, and vice versa. The laws of physics permit both versions to exist. The most rational societal response has been to classify the various applications according to the risk of accident or abuse that each one poses, and then to regulate each application accordingly. The societal response to the tools and products of molecular nanotechnology will be no different. Some MNT-based tools and products will be deemed safe, and will be lightly regulated. Other MNT-based tools and products will be deemed dangerous, and will be heavily regulated, or even legally banned in some cases.

Of course, the mere existence of legal restrictions or outright bans does not preclude the acquisition and abuse of a particular technology by a small criminal fraction of the population. For instance, in the high-risk category, drug abusers obtain and inject themselves with banned narcotics; outlaw regimes employ prohibited poison chemicals in warfare; and rogue nations seek to enter the "nuclear club" via clandestine atomic bomb development programs. Bad actors such as terrorists can also abuse less-heavily regulated products such as fully-automatic rifles or civilian airplanes (which are hijacked and flown into buildings). The most constructive response to this class of threat is to increase monitoring efforts to improve early detection and to pre-position defensive instrumentalities capable of responding rapidly to these abuses, as recommended in 2000 by Freitas[2909] in the molecular nanotechnology context.

The least problematic danger of a new technology is the risk of accident or malfunction. Engineers generally try to design products that work reliably and companies generally seek to sell reliable products to maintain customer goodwill and to avoid expensive product liability lawsuits. But accidents do happen. Here again, our social system has established a set of progressive responses to deal efficiently with this problem. A good example is the ancient technology of fire. The uses of fire are widespread in society, ranging from lightly-regulated matchsticks, butane lighters, campfires, and internal combustion engines, to more heavily regulated home HVAC furnaces, municipal incinerators and industrial smelters. A range of methods are available to deal quickly and effectively with a fire that has accidentally escaped the control of its user. Home fires due to a smoldering cigarette or a blazing grease pan in the kitchen are readily doused using a common household fire extinguisher. Fires in commercial buildings (e.g., hotels) or industrial buildings (e.g., factories) are automatically quenched by overhead sprinkler systems. When these methods prove insufficient to snuff out the flames, the local fire department is called in to limit the damage to just a single building, using fire trucks, water hoses and hydrants. If many buildings are involved, more extensive fire suppression equipment and hundreds of firefighters can be brought in from all across town to hold the damage to a single city block. In the case of the largest accidental fires, like forest fires, vast quantities of heavy equipment are deployed including thousands of firefighters wielding specialized tools, bulldozers to dig firebreaks, helicopters with pendulous water buckets, and great fleets of air tankers dropping tons of fire retardants. (These progressive measures also protect the public in cases of deliberate arson.) The future emergency response hierarchy for dealing with MNT-based accidents will be no less extensive and will be equally effective in preserving human life and property, while allowing us to enjoy the benefits of this new technology. Notes Steen Rasmussen of Los Alamos National Laboratory in New Mexico: "The more powerful technology you unleash, the more careful you have to be."[3107]

6.3.2 Molecular Assemblers Are "Impossible"

The second argument against designing a molecular assembler is that it is simply impossible.[14,15,202-206] According to this argument, artificial programmable self-replicating manufacturing systems cannot be built by human engineers, and therefore any attempt to develop them constitutes wasted effort. This claim conveniently eliminates any concerns that might otherwise be raised by the potential development of nanoweapons systems. In this view, the risks of nanotechnology are intrinsically low, or limited to toxicology risks such as the inhalation of nanoparticles.[235]

Initial arguments against feasibility were sweeping, and based on supposedly universal principles. Molecular assemblers were deemed impossible because thermal noise or quantum effects made molecular machines in general impossible.[202-207] These arguments

---

** Freitas (2000):[2909] "Specific public policy recommendations suggested by the results of the present analysis include: (1) an immediate international moratorium on all artificial life experiments implemented as nonbiological hardware. In this context, 'artificial life' is defined as autonomous foraging replicators, excluding purely biological implementations (already covered by NIH guidelines tacitly accepted worldwide) and also excluding software simulations which are essential preparatory work and should continue. Alternative 'inherently safe' replication strategies such as the broadcast architecture are already well-known...."*

*** Phoenix and Drexler (2004):[3106] "The construction of anything resembling a dangerous self-replicating nanomachine can and should be prohibited."*

lost ground when it was pointed out that biological molecular machines exist, and are able to function despite any limitations that might be imposed by thermal noise or quantum uncertainty. It may be recalled that in 1959, biologist Garrett Hardin[3039] noted that some geneticists called genetic engineering "impossible" as well. Today such criticisms of molecular assemblers survive only among ill-informed authors[3040] who are obviously unfamiliar with the voluminous technical literature on this subject.

More recent arguments concede the feasibility of biological molecular machines but attempt to argue that there are fundamental differences between biological systems and molecular assemblers able to synthesize a wide variety of non-biological materials. For example, in 2001 Vogel[13] wrote: "Future man-made nanosystems will certainly be able to perform a variety of functions, but a robot that is proficient in all three functions — movement in space, recognition of a chemically complex environment, and self-replication — will remain the fabric of dreams." Most notably, in the same year Nobel chemist Richard Smalley wrote in a now-classic quotation:[14] "Self-replicating, mechanical nanobots are simply not possible in our world."* In support of this bold claim, Smalley advanced two objections — the "fat fingers" and "sticky fingers" problems — which are, in reality, objections to mechanosynthesis and not to self-replication.

The "fat fingers" objection is the assertion[14,3041] that "there just isn't enough room in the nanometer-size reaction region to accommodate all the fingers of all the manipulators necessary to have complete control of the chemistry." How many fingers are necessary? The original claim[3042] that "chemistry is the concerted motion of at least 10 atoms" excludes a large part of well-known chemistry and was subsequently expanded[14] to the claim that: "In an ordinary chemical reaction five to 15 atoms near the reaction site engage in an intricate three-dimensional waltz that is carried out in a cramped region of space measuring no more than a nanometer on each side." The supposed need for 15 "fingers" in "ordinary" chemical reactions, and the apparent impossibility of placing 15 probe tips in the small volume of a reaction site was then deemed "fundamental."

But chemical reactions often involve less than five reactants, and frequently involve only two. These two reactants can be brought together with one reactant bound to a substrate and the second reactant positioned and moved by a single "finger" — as has already been demonstrated experimentally, for example, by Ho and Lee,[3054] using an STM. Even if steric constraints near the tool tip made it unexpectedly difficult to manipulate particular individual atoms or small molecules with sufficient reliability, a simple alternative would be to rely upon conventional solution or gas phase chemistry for the bulk synthesis of nanoparts consisting of 10-100 atoms. These much larger nanoparts could then be bound to a positional device and assembled into larger (molecularly precise) structures without further significant steric constraints. This is the approach taken by the ribosome[3043] in the synthesis of proteins: individual amino acids are sequentially assembled into a specific atomically precise polypeptide without the need to manipulate individual atoms (Section 4.2). "Atomically precise" is a description of the precision of the final product, not a description of the manufacturing method. The "fat fingers" problem disappears.

The "sticky fingers" objection is the assertion[14] that "...the atoms of the manipulator hands will adhere to the atom that is being moved. So it will often be impossible to release this minuscule building block in precisely the right spot....these problems are fundamental...." The existence of some unworkable reactions does not preclude the possibility of a great number of workable reactions. If the "sticky fingers" problem** is truly fundamental, then no set of reactions could exist which allows the synthesis of a useful range of precise molecular structures. But we know this is untrue. The ribosome, a ubiquitous biological molecular assembler that suffers from neither the "fat finger" nor the "sticky finger" problem, readily synthesizes the class of atomically precise molecular structures known as proteins using positional techniques (Section 4.2). It is unclear why we should expect there to be no other classes of atomically precise molecular structures that can be synthesized using positional techniques. The experimental observation that ribosomes can synthesize polymers such as proteins under programmatic control appears to contradict the hypotheses that the programmatic synthesis of stiffer polycyclic structures such as diamond is "fundamentally" impossible, and that mechanical assemblers will never be built.

More directly, we can examine both those reactions that have been proposed specifically for use in a mechanical assembler and those reactions that take place using an SPM (scanning probe microscope). Drexler[208] discusses the mechanosynthetic reactions that might be used to synthesize some diamondoid structures of interest. Generally, these involve a single "finger," i.e., a probe tip with a functionalized end that would cause a site-specific reaction on a growing molecular workpiece. Merkle[216] discusses several reactions which involve two, three, and even four reactants bound to the tips of molecular tools. Merkle and Freitas[1,2322-2325] have extended this work, and Freitas[2338] in early 2004 filed the first known patent on diamond mechanosynthesis. A large and growing literature on relevant research work with SPMs — both theoretical[2323-2325,3045-3050] and experimental[2986,3051-3055] — supports the feasibility of site-specific reactions involving a reactive tip structure interacting with a surface or with a molecule on a surface.

Other than the current lack of working molecular assemblers (Section 6.3.3), which might be compared with the lack of rockets able to go to the moon in 1950, there appears to be little evidence to support the claim of impossibility and much evidence to refute it.[16,17] The existence of a wide range of self-replicating biological systems, of new developments in biotechnology and programmable microbes (Sections 4.4 and 4.5) or biobotics,[1875] and the existence of extensive theoretical work on self-replication and nanoscale manufacturing[197-226,2323-2325] strongly support the claim that artificial self-replicating molecular manufacturing systems are feasible, amenable to human design, and will eventually be developed.

Others have argued that artificial self replicating systems are, in general, impossible.[14,204] This claim is contradicted by the fact that compelling examples of artificial replicators exist in the macroscale world (Chapter 3). For example, a number of simple mechanical devices capable of primitive replication from simple substrates have been known since the 1950s,[2] and self-replicating computer programs have been known at least since the 1970s.[2] The Japanese

---

** The utility of organic chemists in commenting on nanosystems engineering may be similar to that of traditional explosives experts commenting on the Manhattan project. Most notably, Fleet Admiral William D. Leahy, Chief of Staff to U.S. President Harry Truman during World War II and formerly Chief of the Naval Bureau of Ordinance during 1927-31 (and later Chief of Naval Operations during 1937-39), maintained until Hiroshima that the atomic bomb being developed under the Manhattan Project would never work. "This is the biggest fool thing we have ever done," he told Truman[2994] in 1945 after Vannevar Bush had explained to the President how the bomb worked. "The bomb will never go off, and I speak as an expert in explosives." Five years later in his memoirs,[2995] he frankly admitted his error.*

*** The only actual proposal for using "sticky fingers" that the authors have been able to locate involves the materials-selective glue idea[3044] proposed in connection with a yet-to-be designed macroscale replicator intended to be built from 0.45-cm machined plastic Lucite blocks. In this informal proposal, a polyethylene hand would grasp the individual Lucite blocks and positionally assemble them into larger structures, after dipping in a methylene chloride glue which "will only bond Lucite to Lucite, but does not bond polyethylene." Presumably the polyethylene hand would later be assembled using a Lucite hand that dips polyethylene building blocks into a glue that does not bond Lucite.*

manufacturing company Fujitsu Fanuc Ltd. briefly operated the first "unmanned" robot factory in the early 1980s,[2] then reopened an improved automated robot-building factory in April 1998[712] that uses larger two-armed robots to manufacture smaller robots with a minimum of human intervention, starting from inputs of robot parts, at the rate of 1000 daughter copies (of individual robots) per year; apparently a different part of the factory uses a distributive warehouse system for automatically assembling the larger robots.[713] Other robotic manufacturers such as Yasukawa Electric[714] also use robots to make robot parts.[711] The manufacturing base of most industrialized countries, of many states or provinces, and even of some individual large municipalities can produce most of the material artifacts of which the base itself is composed, constituting yet another existence proof for artificial or technological self-replication. Finally, the world's first macroscale autonomous machine replicator, made of LEGO® blocks, was built and operated in 2002 (Section 3.23.4). By contrast, the arguments that have been advanced against the feasibility of artificial self replicating systems in general and assemblers in particular[202-205] are of uniformly poor technical quality and display an astonishing ignorance of the relevant literature.

Feasibility can be demonstrated by exhibiting a single feasible design. Impossibility can only be proven by showing that all potential designs are impossible. As there are a vast number of designs that can be imagined, and a potentially even vaster number that have yet to be imagined, the task of proving impossibility is daunting. The great value of impossibility proofs is well understood in computer science, where the impossibility of solving the halting problem is a widely known and very robust result — a result based on rigorous proofs. Knowing that a problem is impossible is very useful, as it means research to solve the problem can be abandoned.

By contrast, attempts to kill research into molecular manufacturing systems by the casual use of the term "impossible," supported by arguments that collapse under even casual scrutiny, and in the absence of any attempt at rigor, are on par with previous claims that flight to the moon was impossible, or that heavier-than-air flight was impossible.

The related claim of impracticality is sometimes advanced on the basis that because evolution required "billions of years" (actually, ~0.8 billion years; Section 5.10) to produce bacteria, it is impractical to expect to design artificial self-replicating assemblers in any time frame relevant to human effort.[3056] However, the same line of reasoning would suggest that jet airplanes are even more improbable than artificial replicators because an even longer ~4.6 billion years of natural evolution were required to produce a Boeing 747 aircraft. Since aircraft do exist, this argument is proven to be false. Human engineers can act with purpose; nature cannot. It is important to note in this context that if the Wright brothers believed that heavier than air flight was theoretically infeasible, they never would have persisted in engineering an airplane. The claims of theoretical infeasibility and the skepticism surrounding the development of an assembler have inhibited both nanotechnology R&D and education.

A more intellectually honest evaluation might note that the time from the first experimental demonstration of a manually-operated macroscale artificial replicator (Penrose Block Replicators, 1957; Section 3.3) to the first experimental demonstration of a fully automatic macroscale artificial replicator (Suthakorn-Cushing-Chirikjian Autonomous Replicator, 2002; Section 3.23.4) was a mere 45 years. The first "manual" assembly of a microscale replicator was achieved by Jeon et al[1860] in 1970 and by Morowitz[1861] in 1974 when they assembled a viable synthetic amoeba organism starting from three[1860] and later five[1861] separate amoeba parts that had been cannibalized from many different organisms. Applying the same 45-year time increment to achieve the first automated assembly of a microscale replicator might suggest an arrival date of 2015-2019 for the first molecular assembler or nanofactory. The first demonstration of artificial bacterium-building should occur within a decade or sooner (Section 4.4), since the first construction of a polio virus from scratch has already been demonstrated, in 2002.[1949] As for molecular assemblers or nanofactories, it appears that the schedule is far more sensitive to budgetary support constraints than to technological difficulty.

6.3.3 Assemblers Have Not Yet Been Demonstrated

A few skeptics have argued[2310] that regardless of whether or not assemblers are "impossible," the fact that they have not yet been demonstrated in the laboratory means that there is no point in talking about them. Others[1427,1428] note that assemblers are at best a very distant goal: "Being able to use an AFM tip to move around xenon atoms on the surface of a single crystal to write a company's logo is indeed a remarkable achievement, but from here to the nanomechanical synthesis of objects shaped into the diamond lattice with atomic precision is a very long way." While a lack of full demonstration to date is of course true, it is also true that the two key functionalities of molecular assemblers — namely, positional atomic-scale mechanosynthesis[3057] and an artificial self-replicating robot with parts-assembly capability (Section 3.23) — *have* already been demonstrated in the laboratory. The principal reason for talking about molecular assemblers and nanofactories is the tremendous benefits that molecular manufacturing would bring (Section 6.3.5).

If this argument was applied to all of engineering research and development, then every technological advance would take us completely by surprise because we would be unable to discuss it until it happened. History serves to challenge this position. As noted elsewhere (Section 6.3.4), many advances were in fact discussed extensively before they were achieved. Many others which were not adequately discussed in advance, such as the possibility of cloning mammals, yielded unpleasant or disruptive surprises. Demanding that no discussion or investigation should occur until results are demonstrated is a philosophical position of fatalism, not a technical argument against any particular technology.

6.3.4 An Early Design Will Not Speed Development

A fourth argument against designing an assembler at this time is that such a design might not speed development. This argument holds that even if we knew a fully detailed and validated design, a design that was in fact physically possible, it would neither advance our state of knowledge nor speed development because our present comparatively primitive experimental abilities are insufficient to build it. Therefore, why bother to create the design? In other words, exploratory engineering should not be done at all — the ability to build nanostructures experimentally ought to be demonstrated before systems-level analysis should be attempted.

This perspective suffers from the misconception of technological determinism: the idea that new technology is developed on a more-or-less fixed schedule, independent of the desires and efforts of those involved. According to this view, humans first traveled to the moon in 1969 because that was when the technology to do so was available. There are two related sub-arguments here: First, that the moon landing could not have been done before 1969, and second, that the moon landing would not have been significantly delayed after 1969 because once the technology was available, it was inevitable that someone would do it.

To the first sub-argument, Robert Goddard's classic 1919 paper describing how a small payload could be sent to the lunar surface[3058] and the existence of early "manned moon rocket" technical design proposals in the 1930s and 1940s[3059] (which included numerous features later adopted in the Apollo Program) established that such machines were plausible. This gave decisionmakers sufficient confidence to proceed with development once the political will and public resources became available for such efforts in the early 1960s, even though these efforts probably could have begun decades earlier. "These developments involve many experimental difficulties, to be sure," Goddard wrote of the proposed moon shot in his 1919 paper, "but they depend upon nothing that is really impossible." He presciently concluded his classical work[3058] as follows: "Although the present paper is not the description of a working model, it is believed, nevertheless, that the theory and experiments, herein described, together settle all points that could seriously be questioned, and that it remains only to perform certain necessary preliminary experiments before an apparatus can be constructed that will carry recording instruments to any desired altitude."

To the second sub-argument, we observe that human astronauts have not visited the Moon in 30 years, even though the technology remains eminently available. Thus the mere availability of a technology does not imply that its usage is inevitable if there is no clear recognition of the benefits of using it.

The claim that a design is useless because we can't immediately build it presupposes that the design will have no influence on our assessment of how easy it is to build. But it seems premature to draw broad conclusions about the difficulty of building something in the absence of a design. In research, it is not uncommon to view a problem as very difficult or even impossible — and yet when the solution is found, the problem, in retrospect, appears quite simple. In the present case, we need at least one worked example before we can begin to reasonably address the question of how hard it is to build an assembler. The answer to this question would seem to depend very much on the proposed designs and the volume of the design space that can be explored. The experience of the present authors is that the "difficult" and "fundamental" problems involved in the design of a molecular assembler succumb when systematic efforts are applied to their solution.

Another important historical example can shed some light on the issues involved. In 1821, Charles Babbage designed the Difference Engine (the first hands-off algorithm-executing machine), and by 1834, Babbage had conceived detailed plans for his even more complex Analytical Engine, intended as a general-purpose programmable computing machine but based entirely on 19th century mechanical technology.[3060-3066] The Analytical Engine was to have a random-access memory consisting of 1000 words of 50 decimal digits each (~175,000 bits), with separate memory and central processing unit (CPU), a special storage unit for the instructions or program, data entry via punched metal cards, and even an output printer.[3061,3062,3065] This ambitious device, though well specified, was never built. (A 2000-part working subsection of Babbage's brass-geared Difference Engine was demonstrated in 1832, and an entire working Difference Engine was reconstructed by historians in 1991, proving that Babbage's design was sound).[3065]

But Babbage's proposals were forgotten* and the development of the stored program computer was delayed by about a century. Was that delay primarily caused by our experimental limitations? Or would a better understanding of the theoretical issues have allowed us to build a stored program computer in the mid 1800s? In short, was the development of the stored program computer in the mid 20th century the result of technological determinism? Or was the timing of this most critical technological development influenced by the somewhat random interplay of ideas and events that took place during the preceding decades? We suspect the latter.

With the advantage of hindsight, we can see that an electrical relay-based programmable digital computer could have been built in the 1850s, or earlier.** The first electromagnet was invented by William Sturgeon in 1825, Joseph Henry built the first electromagnetic signaling relay in 1831, and Samuel Morse exhibited the first compact relay-based telegraphy device in 1837 — just three years after Babbage's Analytical Engine design work. Telegraphy was rapidly commercialized in the 1840s,[3068] with the mature consolidation phase of this 19th-century high-tech industry marked by the founding of Western Union in 1851. Thus by the 1850s, telegraphs were common, electromechanical relays were well known, and the major barrier to implementing a stored program computer was our collective failure to understand how easily it could have been implemented with readily available electromechanical technology. Indeed, the world's first programmable digital computer, built by Konrad Zuse in 1941, used 1,408 electromechanical relays for its 1,408-bit random access memory and another 1,200 relays for its central processing unit.[3069] (Zuse's Z-3 machine computed very slowly, taking 3 seconds to perform a single multiplication). Acknowledging Babbage's 110-year precedence, one computer historian[3070] described the much larger relay-based Mark I, the first American programmable digital computer completed in 1944 by Howard Aiken, as "an electromechanical Analytical Engine with IBM card handling." Had Babbage undertaken a more systematic exploration of the design space for computational engines (e.g., including electromechanical options as well as purely mechanical options), and had he been successful in enlisting the aid of others*** with a clearer exposition

---

** The Report of the Committee of the British Association for the Advancement of Science,[3067] written in 1878 about halfway in time between Babbage and ENIAC, demonstrates that Babbage wasn't entirely forgotten. These mainstream scientists knew exactly what the Analytical Engine could be good for (flexible digital program execution for universal calculation), and that it might be useful in a few special cases. But, they argued, the Engine was incompletely specified, and it was not clear whether practical problems would prevent it from working. Furthermore, it was unknown how much effort would be required or how much it would cost. The final official recommendation read as follows: "Having regard to all these considerations, we have come, not without reluctance, to the conclusion that we cannot advise the British Association to take any steps, either by way of recommendation or other wise, to procure the construction of Mr. Babbage's Analytical Engine and the printing tables by its means. We think it, however, a question for further consideration whether some specialized modification of the engine might not be worth construction, to serve as a simple multiplying machine." Politicians were perhaps less insightful, according to a remark attributed[3112] to Babbage: "On two occasions, I have been asked [by members of Parliament], 'Pray, Mr. Babbage, if you put into the machine wrong figures, will the right answers come out?' I am not able to rightly apprehend the kind of confusion of ideas that could provoke such a question."*

*** An alternative history that might have resulted if Babbage's invention had taken hold a century earlier, including giant computing machines transforming global politics, economics and culture in the 19th century, was examined fictionally by Gibson and Sterling in 1990.[3071]*

**** New and superior technologies can still be torpedoed by bureaucrats. For instance, in 1861, Giovanni Caselli patented the pantelegraph or Universal Telegraph, a machine system for sending and receiving images over long distances by telegraph, with transmitted images reproduced using electrochemistry and signals transmitted using the electromagnetic relays that Babbage had ignored. The pantelegraph was the first prototype of a modern fax machine. Overland links were established between several pairs of European and British cities, with the line between Paris and Lyon handling 5000 faxes during the first year of operation in 1865. Despite the enthusiastic personal interest of Emperor Napoleon III and the formation of a commercial Pantelegraph Society in Paris to promote the device, Caselli "clashed with the French Telegraphs administration which, fearing competition with its ordinary telegraphic network, refused to lower the tariff for handwritten dispatches and even advised taxing such dispatches at a higher rate than ordinary ones. Although the pantelegraph, like today's fax, was perfectly able to transmit written texts correctly, there was a general refusal to allow it any other role than the transmission of a banking signature or a trademark, since this was the only system capable of doing so, and the Telegraphs administration went on to ensure it was gently stifled out of existence."[3072] The fax did not make a comeback until the 1980s. Babbage himself probably won few friends in the British establishment when he published an "unmannerly" pamphlet[2993] denouncing the Royal Society and alleging "that wealthy Tory amateurs had a stranglehold on science policy and were discriminating against socially less well positioned scientists, who were more deserving of support."*

of the potential benefits, it seems quite clear in retrospect that the development of the stored program digital computer could have been accelerated by almost a century.

We expect that the development of the first molecular assembler can be similarly accelerated by a systematic exploration of *its* design space (Section 5.1.9) — an important motivation for the writing of this book (Section 6.5).

This leads to an important related point: the design of a molecular assembler will not represent a static object which is dropped upon an eagerly awaiting scientific community (the so-called "waterfall" or "trickle down" model of development). Instead, the design will lead to a proposal which will promptly be criticized from a variety of perspectives. These criticisms will then be used to evolve a second design better able to address the issues raised by the first design. A likely criticism of the first design might be: "We see how to build components A and B, but C is quite beyond us — change it!" The second proposal will itself attract further criticism, leading to further modifications. The design effort will be ongoing, with the objective of simplifying the design to the point that it can be manufactured using available technology. The people involved in the design effort will not just be familiar with a single design, like Babbage. Rather, they will become knowledgeable about the shape of the design space, the range of system designs that are feasible, and the tradeoffs that can be made to simplify or to change various aspects of the design.

6.3.5 Assemblers Would Be No Better Than Conventional Alternatives

A fifth criticism is that molecular assemblers would not be able to produce products of any great value, and that continued evolutionary advances in existing manufacturing methods will allow us to make everything we could desire by extensions of existing techniques.

This argument receives its greatest support from a very simple fact: we know and understand the value of the products that we can already make, for we use them regularly and understand them at least reasonably well. We have little understanding of the products we have not yet made, and so we question both their feasibility and their value because we have no experience of them. Thus, any product that has not already been made is viewed with suspicion. But the justification of a new manufacturing method is precisely that it can make new products that are of great value — and it is precisely here that our collective understanding is at its weakest. As a consequence, some critics have argued that assemblers will make little contribution to our ability to manufacture useful new products because these critics have but a weak grasp of the truly astonishing range of products that are possible but which have not yet been made.

Fortunately, we have one class of products where molecular manufacturing will clearly let us build new and remarkably valuable products: computers.[208,3074-3078] Computer memories, computer processors, and mass storage will all very obviously benefit from improved manufacturing technologies. Even the poorest informed can understand that computers are dramatically more powerful today than they were a few decades ago, and that this trend is likely to continue for at least many more years. Almost everyone can understand that computer hardware may be pushed to its utmost limits if we are able to arrange atoms in the precise patterns that we desire, rather than the molecularly imperfect patterns that we can make at present.

Even here, though, ignorance can create a fog that thwarts progress. In a conversation with a highly placed head of a governmental research organization, one of the authors [Merkle] found himself explaining that the ability to arrange dopant atoms at specific lattice sites would greatly improve the performance of computer hardware (as compared with the present-day statistical dispersal of dopant atoms in regions of silicon). The highly placed official quite literally did not know if such precision would or would not be helpful.[3079] Ignorance of what has not yet been built creates doubts that sap support, and lends credence to those who advocate doing nothing. There is always a plentiful supply of such advocates.

Computers, of course, are only one of the many revolutionary new applications of molecular nanotechnology. Medical applications will transform healthcare throughout the world.[199,228-235,2910] Here, it is much easier to miss the magnitude of the change that is coming. Disease and sickness are so much a part of our lives that we have a hard time envisioning a day when they may be absent, much as medieval patients would have been hard pressed to envision a modern hospital or the vast improvements that have taken place in health care. The first author's publication of *Nanomedicine* Vol. I[228] in 1999 and Vol. IIA[235] in 2003 are the first steps in conveying to a broader technical audience the raw magnitude of the all-encompassing shift that is coming. No discussion of an individual improvement, or of some particular way to alleviate one particular unhealthful condition, can convey the scope of the medical revolution that is now appearing on the horizon. Book-length expositions are required to bring together in one place our best understanding of the many ways that nanomedicine will improve and expand our lives.

The interested reader is also referred to other sources[2887,2891,2910,3080] for discussions of the many applications of molecular nanotechnology. Those who argue that nanotechnology will bring only modest benefits fail to grasp the magnitude of the changes that are in store, in part because people often have a hard time envisioning the impact of a new technology. We most easily understand what we can see and touch and use directly in our lives. Theoretical extrapolations based on abstract analysis of well-understood physical law is beyond most people, as witness the general rejection of rocket flight[3081] in the early 1900s — even though the basic principles of Newtonian mechanics were well established and the energy that could be derived from chemical rocket fuels was well known.[3058]

6.3.6 Potential Design Errors Make the Analysis Inherently Worthless

A sixth criticism is that an error in some part of a preliminary design could make the entire design unworkable, hence the effort is inherently worthless. Almost certainly, some aspect of any preliminary theoretical design will eventually prove to be unworkable when the design is subjected to greater theoretical or experimental scrutiny. Hence the argument is advanced that any attempt at a design is worthless, because one or more hidden flaws in the specific design might make the entire enterprise infeasible.

This argument ignores the fact that there are usually many possible solutions to a given technical challenge, and more than one way to provide a needed capability. If one approach doesn't work, then another means may be found. The initial design effort then will have been valuable, both because much of it was later found to be feasible and because the precise specification of subsystems allowed and encouraged closer examination of those subsystems, the discovery of the errors within, and the avoidance of that error by other means not originally contemplated. The design will also be useful if it helps to illuminate broad volumes of the design space in which diverse useful possibilities may reside, not all of which suffer from the same identified flaw.

Drexler[208] offers an example of a proposed nanomechanical system that consists of five essential subsystems, each serving a particular function, including: (1) a motor, (2) a power supply, (3) a

Table 6.2. Comparison of macroscale machinery and known nanoscale machinery found in biology (modified from Drexler[197])

Macroscale Machine Component	Device Function	Nanoscale Machine Component (in biology)
Struts, beams, casings	Transmit force, hold positions	Microtubules, cellulose
Cables	Transmit tension	Collagen
Fasteners	Connect parts	Integrins, connexins, etc.
Solenoids, actuators	Move things	Conformation-changing proteins, actin/myosin
Motors	Turn shafts	Flagellar motor
Drive shafts	Transmit torque	Bacterial flagellar rod
Bearings	Support moving parts	Membrane-bound channel complexes in flagellar motor
Containers	Hold fluids	Vesicles, viral capsid
Pumps	Move fluids and ions	Ion transporter pumps, membrane proteins
Conveyor belts	Move components	Vesicular transport along microtubules, RNA moved by fixed ribosome (partial analog)
Clamps	Hold workpieces	Enzymatic binding sites
Tools	Modify workpieces	Metallic complexes, functional groups, transfer RNA
Production lines	Construct devices	Enzyme systems, endoplasmic reticulum, ribosomes
Numerical control systems	Store/read mfg programs	Genetic system in cells

vacuum pump, (4) a pressure sensor, and (5) a gas-tight wall. If we assume that for each subsystem there are 10 equally plausible engineering possibilities that are not mutually exclusive, and if each possibility has an independent 50% probability of working, then the probability that all ten options will fail, leaving no workable choice for a particular subsystem, is only $(0.5)^{10} = 0.001$, and so the probability that a successful combination of all essential subsystems exists is $(1 — (0.5)^{10})^5 = 0.995$. Hence a near certainty may emerge from a combination of possibilities, each of which, individually, is as likely to fail as to succeed.

This argument can be made even stronger when the design itself systematically adopts approaches that can be solved by any of a wide variety of approaches. Present assembler designs are based on the feasibility of subsystems, each of which can be implemented by a wide variety of different methods. For example, the use of positional assembly requires only that some molecular-scale positional device be feasible — if the specific design proposed has some hidden flaw, it can readily be replaced by some other design. As the reader can well imagine, there are a vast number of possible robotic arms, and a vast number of possible molecular positional devices. Only if all possible robotic arms proved infeasible would the system-level proposal fail from this cause.

Similarly, there is a vast space of possible chemical reactions that could be used to build the system. While researchers to date have focused on specific reaction pathways (the better to analyze them in detail), there are many ways to synthesize stiff hydrocarbons and even more ways to synthesize alternative stiff materials which would be suitable for the manufacture of the mechanical design proposals described here and elsewhere. Failure of a specific reaction to work as expected would merely result in the adoption of an alternative synthetic pathway, and even if all methods of synthesizing stiff hydrocarbons were eliminated (which seems a remarkably unlikely prospect, given the wide range of routes by which such structures can and have been synthesized) we would still have available the rest of the periodic table and the resulting combinatorial explosion of possible structures that it enables, from which to choose.

6.3.7 Macroscale-Inspired Machinery Will Not Work at the Nanoscale

A seventh criticism is that designs of molecular machine systems that resemble forms derived from macroscale machinery might not work,[2310] or will be outmoded by better designs in the future because possibly new forms of machinery that might be better suited to the nanoscale have yet to be discovered or invented. There is an even more general objection that things are too wiggly, squishy, and sticky at the nanoscale for any machine-like paradigm to work, and that structures like gears, levers, motors and so on won't work at the nanoscale because "things are just so different at that scale." Many of these objections are primarily intuitive and ignore the fact that nanoscale analogs of macroscale gears, motors, struts, and other mechanical components have all been observed in biology (Table 6.2). Biology demonstrates that many machines, including girders, motors, bearings, ratchets, cables, and so forth are quite recognizable and do in fact work at the nanoscale. So why study diamondoid machines instead of biological machines (Section 4.4), when biology is already known to work? Diamondoid building materials have substantial and useful advantages over biological materials — particularly physical strength, mechanical rigidity, reduced thermal vibrations and friction, chemical inertness and durability, etc. — so these materials are worth studying for nanorobotics applications, and worth working towards.

How can we have any confidence that macroscale-inspired rigid-material machine designs will work at the nanoscale? It is well-known that some macroscale motifs, if implemented in MEMS today, would work poorly if at all. One example is the sliding interface, as might be found in conventional macroscale bearings and pistons, which would become nonfunctional in a contemporary micron-scale MEMS device. One critic[15] notes that nanodevices with such moving parts face the problem of friction and sticking — or "stiction" — because small devices have very large surface/volume ratios. Hence, he concludes, there is no "reason to assume that nanomachines must resemble human-scale machines."

But designers of these nanomachines have made no such assumptions. Rather, they have undertaken detailed mathematical[208,3050] and computational studies[208,222,223] of *de novo* molecular machine components to help ascertain which designs might be expected to function as desired at the nanoscale. For example, recognition of the "stiction" issue dates back to at least 1959 when Feynman[2182] suggested running bearings dry. It was subsequently analyzed in greater detail in 1987 by Drexler,[3049] who examined the symmetry considerations involved in making bearings that exhibit low static friction. The issue was again analyzed in *Nanosystems*,[208] including the more general case of two surfaces sliding over each other. Merkle[3050] also considered specific examples of nanoscale bearings and concluded that properly-designed components having very low static friction should be feasible. Molecular dynamics simulations of atomically-specified nanoscale gear and pump designs by research groups at NASA[222] and CalTech[223] show that these devices should function well even when operated at speeds well in excess of design specifications. Experimental evidence that molecules can rotate freely in an appropriate environment is overwhelming. This evidence includes, for instance, the work of Gimzewski[3082] showing that the rotation of individual molecules on a surface can be stopped or started by changes in the local molecular environment, the work of Cumings and Zettl[3083] demonstrating near-frictionless sliding of nested carbon nanotubes, and the common observations that molecules can rotate freely around a single bond and that even fairly large molecules often move freely on a surface.

Note that bearings and sliding surfaces are often of very low quality when manufactured using existing lithographic methods, involving surfaces that are imperfectly characterized and are, at the molecular scale, very rough. Properly fabricated molecularly precise surfaces should be able to slide over each other with little friction or wear[3083] for extended periods of time. While it is true that "we have a long path to travel before we can produce nanomechanical devices in quantity",[15] this is an assessment of the current primitive state of molecular systems engineering, not a description of a fundamental barrier presented by physical laws.

More generally, the claim that we should not explore molecular scale designs that happen to resemble macroscale designs is ill founded. One basic premise is that positional assembly at the molecular scale should greatly increase the range of molecular-sized structures that we can fabricate. Most existing molecular machines do not use positional assembly (with the notable exception of the ribosome, which employs positional assembly in a rudimentary form; Section 4.2), and hence need not — and do not — deal with the issue of how to position molecular parts under programmatic control.

If we wish to position molecular parts, then we must ask what a molecular-scale positional device should look like. Should it resemble a small STM that uses piezoelectric effects to move in X, Y and Z? The major drawback of this approach is that piezocrystals move only a small percentage of their total length. If we want a range of motion of 100 nm, and if the piezo changes length by 1% when voltage is applied, then our "molecular" positional device will be ~10,000 nm or 10 microns in size. By contrast, a positional device that more closely resembles a macroscale robotic arm might be 200 or 300 nm in size while providing the same range of motion.

In other words, the same basic issues that drive the design of macroscale robotic arms are still present and have a major influence at the molecular scale. If we want a large range of motion in a compact space, then the human arm (which has a range of motion of about 1 meter, and is about 1 meter in length) is not a bad design approach. If we want programmable motion, then joints that can rotate, extend, and contract are very useful. Power subsystems that convert electrical or other forms of energy into rotary and linear motion continue to be useful, and for much the same reason.

Positional assembly at the molecular scale is novel, so we should not expect that it will lead to "familiar" designs (that is, designs that resemble existing well-studied biological systems). Because many of the fundamental design goals and design constraints are similar to the goals and constraints seen in larger designs, we should not be too surprised to find that molecular-scale designs for positional devices often resemble their larger counterparts.

The argument that molecular-scale designs that resemble macroscale designs are "naive" or "unworkable" also reflect a lack of familiarity with the fundamental objectives of positional assembly at the molecular scale. Today's chemistry is based on self-assembly. Therefore it should not be too surprising that those who have spent their entire professional lives learning how to synthesize molecular structures in the absence of positional assembly should find approaches based on positional assembly to seem unusual and unfamiliar.

6.3.8 *The Design Is Too Obvious*

Finally, the complaint may be raised that the design is too simple or too "obvious." While this may at first appear to be a purely aesthetic objection, the complaint actually reveals a biologically-trained mindset that uncritically accepts the underlying assumption that any device capable of replication must be at least as complex as natural replicators (such as living cells) are imagined to be. While mammals are self-replicating and have a genomic complexity of several billion bits, this does not seem significantly more complicated than the most complex human engineering projects — for example, the 2003 release of Microsoft Windows has several tens of millions of lines of code or ~24 billion bits (Section 5.10). Of perhaps greater significance, the simplest biological self replicating systems are in fact much simpler. *Mycoplasma genitalia*, for instance, has a genomic complexity of only 1,160,148 bits (twice the number of base pairs in its DNA;[1867] Table 5.1), so the assumption that biological systems are necessarily complex is incorrect.

Regarding "obviousness" in the legal/commercial context, Berube[3025] also notes that serious cooperative early work in nanoscience may be inhibited because of the current legal regime regarding intellectual property, which may be forcing innovators to resort to trade secrets (rather than public disclosure) as a way to protect their work and "delaying patenting to restrict access to the broad claims a basic patent engenders."

6.4 Specific Goals of a Focused Design Effort

Given that a focused design effort for molecular assemblers would be deemed useful, what should such an effort aim to produce? We believe the results of such an effort ideally should aim to demonstrate feasibility of a specific molecular design: (1) by exemplifying programmable molecularly precise positional assembly and self-replication in a molecular manufacturing system (Section 6.4.1); (2) by exemplifying a simple design (Section 6.4.2), a capable design (Section 6.4.3), and a benign design (Section 6.4.4); and (3) by embodying principles of good design (Section 6.4.5). We conclude with some recommendations for future work (Section 6.4.6).

6.4.1 *Show Feasibility of Molecular Assembler or Nanofactory*

The hallmarks of the molecular assembler are molecularly precise positional assembly coupled with a capacity for massively parallel or replicative manufacturing.

1. **Exemplify Programmable Molecular Positional Assembly.** The first objective requires the designer to embody and illustrate the principles of programmable molecularly precise positional assembly in a specific physical design for a molecular assembler. Manufacturing involves assembling parts, and parts can either be self-assembled, positionally assembled, or assembled by some combination of these two basic approaches. That is, parts are assembled either by (1) allowing the parts to move at random until they "settle in" to the right position (self-assembly), or by (2) actively positioning the parts in the desired location and orientation (positional assembly). Combinations of these two approaches may also used, such as jiggling a pin until it slides into a hole.

   Self-assembly (e.g., Sections 4.1, 4.3, 4.4) is a well-known and extensively studied method of assembling molecular parts.[1436-1440] Positional assembly of molecular parts (e.g., Sections 4.2, 4.5-4.7, 4.9-4.17) is still a relatively new concept.[208] While it has been experimentally demonstrated[3084-3088] that molecules and molecular parts can be positioned and assembled using positional devices such as the SPM (Scanning

Probe Microscope), our ability to positionally assemble molecular parts is still in its infancy. Hence the first purpose of a new design would be to show the great potential of programmable positional assembly of molecular components. For example, our design (Section 4.11.3) employs two 7-degree-of-freedom positional devices (Stewart platforms[208,215]) which, under appropriate programmatic control, could be used to fabricate the entire system.

One consequence of this design objective is that close attention must be paid to the stiffness of the positional device and of other system components in the mechanical loop from the tool tip to the workpiece. At the molecular scale, positional uncertainty caused by thermal noise is a significant design constraint.[208,2324,2325] It is difficult to accurately assemble molecular parts if positional uncertainty is too large, just as it is hard for someone with Parkinson's disease to repair a wristwatch. If positional accuracy is to be maintained, key system structures must be adequately stiff.

2. **Exemplify Self-Replication in a Molecular Manufacturing System.** An equally important objective is to embody and illustrate the principle of self-replication in a specific physical design for a molecular assembler. More broadly, the design objective is to demonstrate the feasibility of a self-replicating manufacturing system. While the theoretical literature on self-replicating systems clearly reveals a wide range of non-biological designs, there is still a general perception that "replicating systems" means "living systems." This perception is grossly in error and lies at the root of much current confusion and misunderstanding about the long-term issues involved in the development and deployment of molecular assemblers.

6.4.2 *Exemplify a Simple Design*

Another important design objective is simplicity. The term "assembler" does not describe a specific design, but a large family of designs. Our objective would not be to describe the best, or the most efficient, or the most flexible, or the fastest possible design. Instead, our objective would be to describe a simple design that satisfies our basic goals of safety and efficacy, while illustrating the use of programmable positional control to achieve flexible manufacturing capabilities and to achieve self-replication or massively parallel operation. It is hoped that the design would serve, among other things, as a theoretical demonstration of concept — a demonstration which must necessarily precede the experimental proof of concept in the laboratory.

1. **Offloading Complexity.** Creating a simple design that is capable of achieving the main objectives requires a general design philosophy which we call "offloading complexity." In this design philosophy (explicitly adopted here), whenever practicable, structures and functions required to be performed by the device are made as simple as possible by transferring as much as possible of the structure or function to outside of the device,[1287] or up to the macroscale.[208] In the Merkle-Freitas example (Section 4.11.3), for instance, rather than using a more complex onboard computer with stored instructions or even a somewhat simpler signal demultiplexor to control the assembler, a far simpler direct-drive control chain is employed onboard the device and the train of control signals is provided sequentially from without. Rather than a more complex indigenous onboard power supply, power is supplied via a simple pressure-driven actuator and source power is generated and transmitted from the outside; and so forth.

We seek to offload functional complexity so that the operations required to be performed by the device and the analyses necessary to rigorously estimate and validate device performance can be made as simple as possible, thus maximizing the probability that the proposed device will work as claimed. We seek to offload structural complexity so that the device is as close as possible to current or foreseeable "manual" molecular construction capabilities, an important step toward addressing the well-known "chicken-or-egg" problem. The principle of offloading complexity is somewhat analogous to the "end-to-end principle" in network design — the concept that intelligence should be placed at the edge of a network to keep the network itself simple, making the technological evolution of the network much more flexible by requiring only a minimum amount of coordination among network owners and users.[3073]

2. **Restriction to Hydrocarbon Materials.** An important design tradeoff results from the conflict between the desire for a manufacturing system able to arrange atoms in most of the ways consistent with physical law, and the desire for onboard structural and functional simplicity. A good compromise seems to be to restrict the system objectives to the synthesis of a diverse range of stiff hydrocarbons. A complete analysis of the reactions by which an assembler converts incoming raw materials into reactive tools used to synthesize molecular structures is greatly simplified if we restrict ourselves to the elements hydrogen and carbon, and further restrict our attention to structures that are relatively stiff (excluding, for example, floppy polymers). The stiff hydrocarbons include a wide enough class of materials to be a very attractive goal — diamond, graphite, and structurally related materials are found in this class. Essentially all mechanical structures can be made from stiff hydrocarbons including struts, bearings, gears, levers, etc. This can be most readily seen by noting that the strength-to-weight ratio of diamond is over 50 times that of steel or aluminum alloys — a single part made of metal could be functionally replaced by a similarly shaped stiff hydrocarbon part. The resulting part would be lighter and stronger than the part it replaced, improving overall performance. The class of stiff hydrocarbons also includes molecular computers which, by today's standards, would be extraordinarily powerful.[208]

A more general assembler, able to manufacture structures which incorporate most of the elements of the periodic table, would be substantially more difficult to analyze. One approach to breaking down the task of building a relatively large and complex structure would be to consider a series of small incremental changes to an exposed surface, the cumulative effect of which would be to manufacture the whole. This implies we must analyze small changes to the exposed surface, presumably by considering small clusters of atoms on that surface. A very minimal cluster might be a single atom and the atoms to which it is bonded. If one atom is bonded to (say) three neighbors, and all four atoms can be any one of about 100 possibilities, then this gives us 100^4 or ~100,000,000 possible clusters. This analysis is crude and likely too small because (a) atoms are often bonded to more than three other atoms and (b) understanding an incremental change to a small cluster often requires examination of atoms farther away than one bond length. Despite its shortcomings, this crude model tells us that we would need to analyze many types of incremental surface modifications before we could reasonably hope to synthesize the full range of structures accessible using this approach.

By contrast, if our structures contain only hydrogen and carbon then the problems of design and analysis become much simpler. Hydrogen can only be bonded to one other atom which, if we exclude hydrogen gas, must be carbon. A carbon atom will usually be bonded to two, three, or four neighboring atoms, which can only be hydrogen or carbon. Our previous crude analysis would assign 2^4 or 16 possible local clusters for carbon. While this can be reduced by considering isomers, it must also be increased to consider interactions that extend beyond a single bond length, e.g., aromatic rings, conjugated systems and the like. In any event, the complexities of analyzing hydrocarbon structures with sufficient accuracy for the purposes discussed here is tractable with present capabilities. We can cut short the combinatorial explosion before it begins.

While this rather drastic pruning makes the problems of designing and analyzing a hydrocarbon assembler more tractable, it does not directly address the feasibility of more general assemblers. Smalley[3041] in particular has argued that a "completely universal" assembler is impossible, though he has also admitted[3089] that "most interesting structures that are at least substantial local minima on a potential energy surface can probably be made one way or another." Smalley argues that a small set of molecular tools will be unable to catalyze all the reactions needed to synthesize the remarkably wide range of structures that are possible. We agree with these assessments. Success may require the use of a great many custom-made catalytic structures.

Given the remarkable size of the combinatorial space of possible molecular structures, it seems likely that at least some members of this space will resist direct synthesis by an assembler equipped with a relatively modest number of molecular tools. However, even if we assume that a substantial percentage of the space is inaccessible via this route (an assumption as yet lacking any clear support) the remaining "small" fraction would still include structures of enormous economic value. Even the ability to manufacture only the highly restricted range of structures defined by the stiff hydrocarbons would usher in a revolution in manufacturing.

Further research aimed at clarifying the range of structures amenable to synthesis by positionally controlled molecular tools is urgently needed. Ideally, this would include not only the proposal and analysis of particular sets of molecular tools and the range of structures they could reasonably make, but also proposals of structures which could not be synthesized by the use of positionally controlled molecular tools. One example of an "impossible" structure is a cubic meter of flawless diamond — before its manufacture could be finished, background radiation would have introduced flaws. Drexler (ref. 199, p. 246) argued that it should be possible to define a structure which would be stable if complete but unstable when almost complete, a sort of molecular stone arch.[3090] However, a specific, relatively small, stiff and stable structure that can reasonably be viewed as "impossible" to synthesize using positionally controlled tools has not yet been proposed. While it seems likely that at least some such structures must exist, our understanding of this issue would be greatly improved by specific examples.

3. **Design for Assembly.** Because the unitary construction of interlocked parts can be extremely difficult, it will likely be necessary to fabricate individual parts which must then be assembled into completed structures. For this reason, an important objective is "design for assembly" — the idea that among numerous available design alternatives for a given machine part, the one that is easiest to physically assemble with other parts into desired structures should be preferred over other parts and parts combinations that may be more difficult to assemble. Design for manufacturing/assembly (DFM/A)[3091-3098] and computer-aided assembly planning[3099,3100] are recognized specialties in conventional manufacturing engineering, and these emerging disciplines will likely play an important future role in molecular manufacturing as well.

4. **Design for Analysis and Validation.** As a practical matter, the chosen design should be accessible to analysis by currently available computational tools for molecular modeling and simulation. The design should be mechanically simple, thus readily permitting basic static, kinematic,[3101] and dynamic analyses. It should employ the minimum number of physical or chemical processes that have not yet been validated experimentally. In short, the best design proposal for a molecular assembler will be one that can be validated as correct — or likely to be correct — using our present-day analytical knowledge base.

6.4.3 Exemplify a Capable Design

For a proposed molecular assembler design to be acceptable, it must exhibit several elementary capabilities:

1. **Bootstrap-Capable System.** It should be obvious that the system design will enable the manufacture of devices of similar or different architecture that can be scaled to larger sizes. Even if the original design describes only a very small device (e.g., with typical dimensions of ~100 nanometers), the manufacturing system, once built, should clearly be capable of "bootstrapping" larger and more complex devices, extending our capabilities beyond the submicron scale and beyond other architectural limitations of the initial system.

2. **Ease of Reprogramming.** Molecular assemblers should be able to readily change what they are manufacturing, thus exhibiting ease of reprogramming.[209] For a general manufacturing system, we should be able to redirect the manufacturing process quickly and rapidly in response to changing demand, once a sufficient factory mass or number of device generations has been replicated. Additionally, numerous software issues must be resolved, including methods of rigorously controlling and coordinating the activities of trillions of simultaneously operating nanoscale manipulators for mechanosynthesis with high reliability and flexibility.

3. **Maximum Geometric Accessibility to Products During Manufacture.** Positional manufacturing manipulators should have the greatest possible geometric access to the object being manufactured. Designs are favored which give greater access to the parts being manufactured, and which permit a wider range of tools and synthetic methods to be used. This objective is one that can be applied during the geometric design of the system, and which is largely independent of the specific mechanosynthetic reactions used to fabricate the product. Satisfaction of this objective also implies that the design can be adapted to other systems of greater complexity (regardless of size).

4. **Maximum Reliability During Operation.** Within the constraints of the limited technologies employed in early designs, the molecular assembler should operate as reliably as possible. The required reliability of subsystems depends on the overall reliability requirements of the entire system, and on the number of subsystems. Even the earliest systems should have a probability of successful replication of at least 99% per replication cycle. Furthermore, the system architecture should be chosen such that the failure of daughter units has minimal impact on the operation of the remaining units that continue to function

without error. In this regard, a unit replicator motif is more clearly failure tolerant than a factory replicator motif. The isolation of a failure to a single unit replicator is more clearly feasible than the isolation of a failure in a factory. Continued satisfactory functioning of a factory in the face of a failure would require a more sophisticated failure isolation strategy and would benefit greatly from a method for switching out or circumventing the failed module.[2334]

6.4.4 *Exemplify a Benign Design*

An acceptable molecular assembler or nanofactory design should be safe, incapable of "natural evolution," and pollution-free.

1. **Demonstrate the Design is Safe.** The system design should be inherently safe (Section 5.11), in the sense that it should not pose the kinds of extraordinary dangers that some have imagined are inevitable for replicating systems.[2909] One primary route for insuring this is to employ the broadcast architecture for control.[209] As discussed in Section 4.11.3.3, the broadcast architecture virtually eliminates the likelihood that the system can replicate outside of a very controlled and highly artificial setting. The design should not describe a replicator that will directly compete with humans, or other biological entities, for the resources necessary for production or self-replication. Note that while a diamondoid molecular assembler would primarily employ carbon atoms in its construction, and carbon is also the principal atom used in biology, the carbon source for assemblers is not complex organic molecules and structures but rather the simplest hydrocarbons such as acetylene or butane, hence such assemblers will not be competing with biology for carbon resources.
2. **Design for Nonevolvability.** The system design should not permit any capacity for endogenous evolution of new structures or new capabilities, as discussed in Sections 2.1.5, 5.1.9 (L), and 5.11.
3. **Clean Manufacturing and Pollution-Free Operation.** Another important design objective is to minimize or eliminate all material waste products generated by replicative or productive activities. Components, subsystems and systems should not be needlessly thrown away during the replication or manufacturing cycle. The source of this objective is not mere environmentalist sentiment and aesthetics, but rather a strong practical desire for manufacturing efficiency. The greater the amount of waste that is produced, the more machine operations (both onboard and offboard) must be devoted to handling and disposing of this waste, which increases manufacturing time per unit mass of product, imposes greater burdens on materials import and export subsystems, produces more waste heat, and modestly increases the possibility of device failure because of the extra processing and transport steps that must be successfully performed. A manufacturing system which produces zero pollution, as exemplified by the Merkle-Freitas Hydrocarbon Molecular Assembler (Section 4.11.3), would be extremely desirable.

6.4.5 *Embody Principles of Good Design*

Any proposed design should embody the many principles of good engineering design, of which there is space here to briefly mention only a few:

1. **Assumptions and Design Tradeoffs Explicitly Stated.** An important principle of good design is to make all assumptions and design tradeoffs explicit. This helps readers calibrate the proposed design against their own understanding of the technological possibilities, illuminates areas most needing further research, and helps others who may wish to adopt different sets of tradeoffs in hopes of exploring other equally promising volumes of the molecular assembler design space.
2. **Seek Broad "Attractors" in the Design Space.** Wherever possible, design solutions should be chosen from sets of possible design choices which occupy the broadest possible volume of design space. Such solutions therefore coexist with many closely related viable design alternatives, allowing both flexibility and robustness in the final design. The demonstrated existence of adequate "design space" (Section 5.1.9) is the single most important reason for believing that feasible designs for molecular assemblers exist. Also important is the concept of modular design and the feasibility of multiple alternative implementations of a given module, with the avoidance of overly "clever" designs that try to solve too many problems at once.
3. **Exemplify Backward Chaining in Design.** Many existing designs for molecular assemblers are more complex and appear more difficult to manufacture than the Merkle-Freitas design (Section 4.11.3) — a design which is simpler while still exemplifying the principle of backward chaining (Section 6.2.1) in design. A simple design such as this should help pave the way toward future designs which will be simpler still, and even more amenable to manufacture, once further efforts at additional backward chaining have been made.

   For example, the Merkle-Freitas design was chosen for its likely intermediate position in the design and development timeline for molecular assemblers. It appears to be one of the least complicated assemblers that could conveniently be specified to molecular detail and yet possesses sufficient capability to allow for the design and manufacture of progressively more complex and capable assembler systems, leading eventually to a molecular manufacturing system of very generalized capability. On the other hand, the same system could be sufficiently precisely specified that it would also permit convenient backward chaining to simpler pre-assembler system designs, a process that is hoped would eventually merge with our ever-expanding contemporary nanoscale technology base, finally providing a clear and complete pathway for the development for molecular manufacturing systems.
4. **Buildability of the Design.** Buildability is an explicit design objective. In the broadest sense, a design may be said to be buildable if, given the proper manufacturing tools and techniques, it could be expressed in hardware. A design which is buildable in this broadest sense must violate no known laws of physics or chemistry and should reflect customary principles of sound engineering design. In a more restrictive sense, a design might also be considered feasible to build if, given certain foreseeable extensions of current technology in directions that can readily be envisioned today, it could be expressed in hardware using those foreseeable technological extensions. In the narrowest sense, a design might be considered buildable only if it can be built in the laboratory or factory today, using nothing but currently available techniques and existing technology and equipment with no further improvements. Buildability in this most narrow sense should not be an objective of a focused design effort intended to demonstrate feasibility of a molecular assembler. Rather, the principal objective should be to create a design that is buildable in the more restrictive sense. This design can then be used, first, to guide the development of successor designs which more closely approach today's building techniques, and second, to simultaneously guide the development of new building techniques that can more closely approach the designs that we believe would be

useful to build, until a sufficient overlap arises between these two sets that it becomes possible to build, as physical hardware, the first working molecular assembler.

5. **Specificity of the Design.** A good system design should describe all important components, systems, and operations with enough specificity to permit rigorous analysis and evaluation by competent engineers. For example, Merkle[211] has described the wide range of details which should be present in any serious molecular assembler design proposal. These details include: (1) the type and construction of the computer, (2) the type and construction of the positional device, (3) the set of chemical reactions that take place at the tip, (4) how compounds are transported to and from the tip, (5) how the compounds are modified (if at all) before reaching the tip, (6) the class of structures that can be built, (7) the environment in which the device may operate, (8) the method of providing power, (9) the requirement (or not) for a barrier that partitions internal and external environments, (10) the type of barrier that can prevent unwanted changes in the internal environment in the face of changes in the external environment, (11) the nature of the external and internal environments, (12) the transport mechanisms that move material across the barrier, (13) the transport mechanism used in the external environment, and (14) a mechanism that allows the assembler to receive broadcast instructions. (Notes Merkle:[211] "The presence of a receiver is not mandatory for the manufacture of interesting structures (as demonstrated by a fertilized egg), but it is extremely useful if we are considering a general purpose device able to make a wide variety of different products. Not only does a receiver allow us to re-program the assembler for specific tasks, it also allows us to significantly simplify the computational element.")

6.4.6 Systems and Proposals for Future Research

Molecular manufacturing is a field of engineering, and the design of molecular assemblers and nanofactories will require expertise in molecular systems engineering. According to a concise definition[3105] offered by the University College London Centre for Systems Engineering:

> *Systems engineering is the branch of engineering concerned with the development of large and complex systems, where a system is understood to be an assembly or combination of interrelated elements or parts working together toward a common objective.*
>
> *Systems engineering focuses on: the real-world goals for, services provided by, and constraints on such systems; the precise specification of system structure and behavior, and the implementation of these specifications; the activities required in order to develop an assurance that the specifications and real-world goals have been met; [and] the evolution of such systems over time and across system families. It is also concerned with the processes, methods and tools for the development of systems in an economic and timely manner.*

Economically viable molecular manufacturing systems based on molecularly precise massively parallel assembly are likely to take longer to develop than the usual three to five year time horizon of the private sector.[3102] The private venture capital sector has shown considerable enthusiasm for funding nanoscale science and engineering projects that focus on novel electrical or physical properties of nanoscale materials. But they are not focusing on the high-risk, high-payoff opportunity of developing molecular manufacturing machine components and systems with complex kinematic nanomachinery. There are some European and Japanese initiatives to develop molecular manufacturing components and systems. The key rationale for U.S. government funding is that molecular manufacturing might not happen first in the U.S., or will happen much more slowly in the U.S., if we rely on the private sector for initial R&D stage funding. The question of who develops this technology first has profound economic, security, military, and environmental significance.

A successful, field-proven, molecular manufacturing system that might be deployed in the mid to longer time frame could be described and analyzed today. Such a system would almost certainly be composed mostly of systems and subsystems that are not experimentally accessible at present, for the simple reason that we cannot yet build the relevant components. But if we are to think about and analyze systems that we cannot build today, and if we are to do so with any certitude, then we must initiate a carefully conceived theoretical and computational R&D program expressly for this purpose. Existing tools in computational chemistry can be harnessed to analyze molecular structures, regardless of whether or not those structures are immediately buildable. Computational modeling of known experimentally accessible structures gives us confidence about the capabilities (and limitations) of the modeling software, and permits us to evaluate structures that have not yet been made — and perhaps cannot directly be made — using our current early 21st century technology base.

The value of such theoretical and computational work, particularly when used to assess systems that exceed our immediate experimental capabilities, is sometimes debated. But the alternative is to abandon active investigation of systems and structures that cannot be built today. Inability to think systematically about what cannot yet be built is very likely to delay our ability to build it. If we are to build machine-phase molecular manufacturing systems in the next two decades — systems that are experimentally inaccessible today — then methodical design work on such systems is both necessary and urgent.[3103]

It is important to reiterate the need to develop and analyze *systems*. The existing evaluation of scientific research is effective in considering specific issues, but is much less effective in generating (possibly complex) systems proposals for engineering assessment and analysis. The story of the scientist who *discovers* some new and useful property of matter after accidentally leaving the Bunsen burner turned on while away at lunch is well known. But the story of the engineer who accidentally *develops* a computer or Saturn V booster is not only unknown, but seems remarkably unlikely.

If — as we believe — the successful development of machine-phase molecular manufacturing *systems* requires the design of massively parallel systems (with some proposals calling for the design of self-replicating systems) then we need to explicitly create programs that solicit systems proposals — proposals that can reasonably be expected to fulfill the goals of molecular manufacturing as outlined above. Systems proposals can be analyzed by theoretical and computational tools that examine the systems as a whole, together with the subsystems and components from which they might be composed.

6.5 Focusing on Molecular Assemblers

According to Merkle,[3104] the broad goals of nanotechnology — the ability to inexpensively arrange atoms in most of the ways permitted by physical law — are now widely accepted. But it is not enough to agree that heavier than air flight is possible, nor is it sufficient to believe that some as-yet unspecified design based on rockets can reach the moon, nor does the abstract realization that mass can be converted to energy change the course of history. We need to move to the next step: the Wright brothers, the Apollo Program, the Manhattan Project. We need to translate abstract agreement into a focused and well-funded project.

Nanosystems[208] gave us a persuasive feasibility argument for assemblers, but provided no design for a specific assembler. For every fundamental design problem, *Nanosystems*[208] gave us several feasible solutions — but never picked one specific solution. Indeed, one of the main conclusions of this work was that we could have confidence that assemblers were feasible precisely because there were many solutions to every problem. While it is difficult to be absolutely certain that a specific solution will work, when there are many possible solutions available it's almost certain that at least one of them will work.

We've seen continued work on specific aspects of assembler design but we haven't seen a complete design. Such a design (and accompanying analysis) is feasible today, but a complete design will require the work of a coordinated team of people for some years. We need to explore the space of possible designs, analyze at least some designs in full detail, and then use those designs as a focal point for further development. We could start today, but as yet, we have not.

The major consequence of this failure is continuing delay, much of which will be caused by a persistent confusion about "what is an assembler." While we are encouraged that all the fundamental problems can be solved, we don't yet have a single design or preferred embodiment that selects a specific solution for each problem and integrates those specific solutions into a single unified system for more rigorous analytical testing. Perhaps more seriously, there is the fog and uncertainty created by mental confusion and misunderstanding. People have a hard time grasping complex arguments and abstract conclusions, and when we are hearing new ideas for the first time it's very easy to get confused. For instance, flight to the moon was once thought to be impossible because "there is no air to push against" in the vacuum of space. The reasoning: Airplane wings push against air, propellers push against air, helicopter blades push against air — so surely the proposed space rockets were meant to push against air? But there is no air in space! Thus can our experience with familiar things mislead us when we consider fundamentally new ideas.

A project with many people must have a clear, detailed, and comprehensive description of both the goal and how to achieve it. We need at least one design for an assembler with all the kinks worked out, all the irritating little design issues settled, all the potential sticking points resolved. Without this, any effort to build an assembler will deteriorate into chaos and confusion as the people involved find themselves working at cross purposes — possibly without even realizing it. For example, if we started out to build a heavier-than-air flying machine lacking a complete plan, and one person designs the blades for a helicopter while another works out the wings of an airplane and a third person analyzes propelling the device by throwing sticks of dynamite out the rear and exploding them, the result will be chaos.

Right now, the detail that we can achieve in a system design is limited by the fact that serious analytical efforts have so far been restricted to small teams of one or a few people. We could significantly increase the detail of the design by increasing the number of people working on it, provided they are the right people. A dozen people, properly coordinated, could start to provide us with coherent system designs having a level of detail that would give us greater collective clarity in understanding the goal and a greater ability to determine the developmental pathways for reaching it.

Besides pursuing designs in more depth and detail, we should also examine systems that differ radically in their approach and assumptions. We can explore the design space (Section 5.1.9) seeking designs that are, for example, easier to build. Consider again the case of the Analytical Engine, designed by Babbage in the 1830s (Section 6.3.4). Although it was the conceptual foundation for the single most important technological development of the 20th century (programmable digital computers), Babbage's design was never built nor was there any systematic exploration of possible alternatives. Looking back with the advantage of perfect hindsight, we can clearly see what Babbage and the rest of the world missed: electromechanical relays. Relays were known in the 1830s and were widely employed during the 1840s in telegraphy. Had Babbage and others systematically surveyed the complete design space for "Analytical Engines," they might have realized that a relay-based computer would be relatively easy to build and quite practical. But they didn't, and so they missed an opportunity of historic magnitude — as did the rest of humanity, who lost the benefits of an earlier implementation of digital computers.

Let's not miss another opportunity.

APPENDIX A

Data for Replication Time and Replicator Mass

Data for replication time (τ) as a function of replicator mass (M) for 126 biological species,[2600] 1 chemical species,[1372] and 9 actual or proposed artificial kinematic replicating systems across a size range spanning nearly 20 orders of magnitude, drawn from numerous sources (most appreciatively the major contribution by Allison and Cicchetti),[2600] appears in chart form in Figure 5.6 and in tabular form below.

Data for tree mass are based on tabulated data for mature trunk diameter D_{trunk} and mature tree height H_{tree}. Tree trunk is taken as a uniform cylinder with diameter and length of dimensions D_{trunk} and H_{tree}, with overall tree density ρ_{tree} ~700 kg/m^3, and the total mass M of the tree is taken as twice the mass of the trunk. Data for tree replication time are the time to first flowering. Data for mammals and birds are gestation time, not time to first reproduction. Data for protozoa and bacteria are inverse cell division frequency. Data for viruses are time to completion of first replica following infection. Bacterial ribosome replication time estimated by assuming ribosomal nucleotides have an approximately similar assembly rate (~15-40 residues/sec) as ribosome-assembled ribosomal peptides. Some data represent an average or typical value within a range (that is not shown).

Name or Type of Replicator	Classification	Replicator Mass, kg (M)	Replication Time, sec (τ)
Giant sequoia	Tree	1,289,225	1.88×10^9
Freitas self-replicating interstellar probe	Manmade Machine	443,000	1.69×10^9
Blue whale	Mammal	108,000	2.76×10^7
NASA self-replicating lunar factory	Manmade Machine	100,000	3.14×10^7
Western larch	Tree	46,206	9.42×10^8
White fir	Tree	44,135	1.10×10^9
White oak	Tree	31,713	6.28×10^8
Humpback whale	Mammal	30,000	2.96×10^7
Pecan	Tree	23,118	3.14×10^8
American elm	Tree	20,536	4.71×10^8
Eastern white pine	Tree	17,014	3.14×10^8
White ash	Tree	14,595	6.28×10^8
Black walnut	Tree	13,038	3.77×10^8
American beech	Tree	12,099	1.26×10^9
Eastern hemlock	Tree	11,676	9.42×10^8
Black cherry	Tree	9908	3.93×10^8
Red alder	Tree	8807	3.14×10^8
African elephant	Mammal	6654	5.57×10^7
Northern white cedar	Tree	5894	9.42×10^8
White spruce	Tree	5224	3.93×10^8
Northern catalpa	Tree	4804	3.14×10^8
Sweet birch	Tree	3523	1.26×10^9
American holly	Tree	3423	1.57×10^8
Quaking aspen	Tree	3002	1.57×10^8
Asian elephant	Mammal	2547	5.39×10^7
Eastern red cedar	Tree	2387	3.93×10^8
Black willow	Tree	1751	3.14×10^8
Wild water buffalo	Mammal	1000	2.76×10^7
Flowering dogwood	Tree	570	1.57×10^8
Giraffe	Mammal	529	3.46×10^7
Horse	Mammal	521	2.90×10^7
Cow	Mammal	465	2.43×10^7
Okapi	Mammal	250	3.80×10^7
Gorilla	Mammal	207	2.18×10^7
Pig	Mammal	192	9.94×10^6
Donkey	Mammal	187	3.15×10^7
Brazilian tapir	Mammal	160	3.39×10^7

continued on next page

Name or Type of Replicator	Classification	Replicator Mass, kg (M)	Replication Time, sec (τ)
Boto river dolphin	Mammal	100	2.89×10^{7}
Jaguar	Mammal	100	8.64×10^{6}
Gray seal	Mammal	85.00	2.68×10^{7}
HUMAN (female)	Mammal	62.00	2.31×10^{7}
Sheep	Mammal	55.00	1.30×10^{7}
Chimpanzee	Mammal	52.16	1.99×10^{7}
Orangutan	Mammal	40.00	2.15×10^{7}
Gray wolf	Mammal	36.33	5.44×10^{6}
Kangaroo	Mammal	35.00	2.85×10^{6}
Goat	Mammal	27.66	1.28×10^{7}
African wild dog	Mammal	25.00	6.05×10^{6}
Lackner-Wendt auxons	Manmade Machine	20.00	1.20×10^{7}
Roe deer	Mammal	14.83	1.30×10^{7}
Baboon	Mammal	10.55	1.56×10^{7}
Patas monkey	Mammal	10.00	1.47×10^{7}
Rhesus monkey	Mammal	6.800	1.42×10^{7}
Raccoon	Mammal	4.288	5.44×10^{6}
Red fox	Mammal	4.235	4.49×10^{6}
Vervet	Mammal	4.190	1.81×10^{7}
Yellow-bellied marmot	Mammal	4.050	3.28×10^{6}
Rock hyrax (*Procavia hab*)	Mammal	3.600	1.94×10^{7}
Nine-banded armadillo	Mammal	3.500	1.21×10^{6}
Water opossum	Mammal	3.500	1.04×10^{7}
Arctic fox	Mammal	3.385	5.18×10^{6}
Cat	Mammal	3.300	5.44×10^{6}
Echidna	Mammal	3.000	2.42×10^{6}
Rabbit	Mammal	2.500	2.68×10^{6}
Tree hyrax	Mammal	2.000	1.73×10^{7}
North American opossum	Mammal	1.700	1.04×10^{6}
Phanlanger	Mammal	1.620	1.47×10^{6}
Slow loris	Mammal	1.400	7.78×10^{6}
Mountain beaver	Mammal	1.350	3.89×10^{6}
Chicken	Bird	1.133	1.90×10^{6}
Guinea pig	Mammal	1.040	5.88×10^{6}
African giant pouched rat	Mammal	1.000	3.63×10^{6}
Drexler desktop factory	Manmade Machine	1.000	3.60×10^{3}
Jacobson train replicator	Manmade Machine	1.000	1.00×10^{2}
Arctic ground squirrel	Mammal	9.20×10^{-1}	2.16×10^{6}
Tenrec	Mammal	9.00×10^{-1}	5.18×10^{6}
European hedgehog	Mammal	7.85×10^{-1}	3.63×10^{6}
Rock hyrax (*Hetero. b*)	Mammal	7.50×10^{-1}	1.94×10^{7}
Suthakorn LEGO® replicator	Manmade Machine	5.00×10^{-1}	1.35×10^{2}
Owl monkey	Mammal	4.80×10^{-1}	1.21×10^{7}
Chinchilla	Mammal	4.25×10^{-1}	9.68×10^{6}
Penrose blocks replicator	Manmade Machine	3.00×10^{-1}	2.00×10^{1}
Rat	Mammal	2.80×10^{-1}	1.81×10^{6}
Galago	Mammal	2.00×10^{-1}	1.04×10^{7}
Hawk	Bird	2.00×10^{-1}	3.11×10^{6}
Mole rat	Mammal	1.22×10^{-1}	2.59×10^{6}
Golden hamster	Mammal	1.20×10^{-1}	1.38×10^{6}
Tree shrew	Mammal	1.04×10^{-1}	3.97×10^{6}
Ground squirrel	Mammal	1.01×10^{-1}	2.42×10^{6}
Hamster	Mammal	9.60×10^{-2}	1.38×10^{6}
Eastern American mole	Mammal	7.50×10^{-2}	3.63×10^{6}
Musk shrew	Mammal	4.80×10^{-2}	2.59×10^{6}
Sparrow	Bird	2.80×10^{-2}	1.21×10^{6}
Big brown bat	Mammal	2.30×10^{-2}	3.02×10^{6}
Mouse	Mammal	2.30×10^{-2}	1.64×10^{6}
Gecko	Reptile	1.00×10^{-2}	8.21×10^{6}
Little brown bat	Mammal	1.00×10^{-2}	4.32×10^{6}
Lesser short-tailed shrew	Mammal	5.00×10^{-3}	1.86×10^{6}
Hummingbird	Bird	3.15×10^{-3}	1.30×10^{6}
Honeybee (*Apoidea apis*)	Insect	1.00×10^{-4}	2.07×10^{6}
Spiders	Insect	1.00×10^{-4}	9.07×10^{5}
Ladybug	Insect	5.00×10^{-5}	2.59×10^{6}
Fruit fly (*Drosophila*)	Insect	1.05×10^{-6}	1.04×10^{6}
Stentor coeruleus (Ciliata)	Protozoan	4.00×10^{-8}	7.78×10^{4}
Chalcid wasp (*Encarsia formosa*)	Insect	2.50×10^{-8}	7.78×10^{5}

continued on next page

Name or Type of Replicator	**Classification**	**Replicator Mass, kg (M)**	**Replication Time, sec (τ)**
Paramecium aurelia (Ciliata)	Protozoan	2.00×10^{-10}	1.20×10^{5}
Paramecium aurelia (Ciliata)	Protozoan	2.00×10^{-10}	4.28×10^{4}
Didinium nasutum (Ciliata)	Protozoan	1.00×10^{-10}	2.40×10^{4}
Euglena gracilis (Mastigophora)	Protozoan	1.10×10^{-11}	2.47×10^{4}
Chilomonas paramecium (Mastigophora)	Protozoan	6.00×10^{-12}	2.47×10^{4}
Azobacter chroococcum	Bacterium	4.00×10^{-15}	1.98×10^{3}
Lactobacillus acidophilus	Bacterium	2.30×10^{-15}	4.59×10^{3}
Clostridium botulinum	Bacterium	2.30×10^{-15}	2.10×10^{3}
Shigella dysenteriae	Bacterium	2.00×10^{-15}	1.80×10^{3}
Mycobacterium tuberculosis	Bacterium	1.80×10^{-15}	5.17×10^{4}
Bacillus subtilis	Bacterium	1.40×10^{-15}	1.74×10^{3}
Mitochondrion	Cell Organelle	1.19×10^{-15}	7.20×10^{3}
Salmonella typhosa	Bacterium	1.10×10^{-15}	1.70×10^{3}
Corynebacterium diphtheriae	Bacterium	1.00×10^{-15}	2.04×10^{3}
Staphylococcus aureus	Bacterium	7.30×10^{-16}	1.77×10^{3}
Erwinia carotovora	Bacterium	6.00×10^{-16}	2.97×10^{3}
Escherichia coli	Bacterium	5.00×10^{-16}	8.88×10^{2}
Streptococcus lactis	Bacterium	4.20×10^{-16}	2.22×10^{3}
Diplococcus pneumoniae II	Bacterium	3.00×10^{-16}	1.68×10^{3}
Diplococcus pneumoniae I	Bacterium	3.00×10^{-16}	1.49×10^{3}
Aerobacter aerogenes	Bacterium	2.00×10^{-16}	1.84×10^{3}
Pseudomonas pyocyanea	Bacterium	1.30×10^{-16}	1.95×10^{3}
Vibrio comma	Bacterium	1.00×10^{-16}	1.78×10^{3}
Merkle-Freitas HC Molecular Assembler	Manmade Machine	3.91×10^{-18}	1.00×10^{6}
Influenza B	Virus	5.00×10^{-19}	3.24×10^{4}
Influenza A	Virus	5.00×10^{-19}	2.43×10^{4}
Swine influenza	Virus	5.00×10^{-19}	2.16×10^{4}
T4 bacteriophage	Virus	3.00×10^{-19}	7.70×10^{2}
Drexler manipulator arm	Manmade Machine	1.00×10^{-19}	5.00×10^{0}
Bacterial ribosome 70S	Cell Organelle	4.00×10^{-21}	4.30×10^{2}
Plant viroid	Macromolecule	2.00×10^{-22}	8.50×10^{1}
R3C ligase ribozyme	Chemical Replicator	1.15×10^{-22}	5.46×10^{3}

Design Notes on Some Aspects of the Merkle-Freitas Molecular Assembler

> *Self-replicating, mechanical nanobots are simply not possible in our world.*
> – Richard E. Smalley, September 2001[14]
>
> *When a scientist says something is possible, they're probably underestimating how long it will take. But if they say it's impossible, they're probably wrong.*
> – Richard E. Smalley, October 2000[3115]

B.1 Geometrical Derivation of Assembler Dimensions

A preliminary design iteration revealed that the physical dimensions of the proposed molecular assembler are constrained by the choice of 4 box-specific geometrical parameters and 7 additional geometrical parameters related to the operation of the interior Stewart platform manipulators, the X-axis elevator upon which the manipulators ride, and the piston. Choosing a priori values for these 11 parameters establishes all remaining major physical dimensions of the system. In the following scaling analysis, the exterior physical dimensions of the proposed molecular assembler hull are (X_{ext}, Y_{ext}, Z_{ext}) with enclosed exterior volume $V_{ext} = X_{ext} Y_{ext} Z_{ext}$ and external surface area $S_{ext} = 2 (X_{ext} Y_{ext} + X_{ext} Z_{ext} + Y_{ext} Z_{ext})$, and the internal physical dimensions of the assembler hull are (X_{int}, Y_{int}, Z_{int}) with enclosed interior volume $V_{int} = X_{int} Y_{int} Z_{int}$ and internal surface area $S_{int} = 2 (X_{int} Y_{int} + X_{int} Z_{int} + Y_{int} Z_{int})$, using the coordinate system as defined by Figure B.1.

From simple geometry, $Y_{ext} = Y_{int} + 2w_{thick}$ and $Z_{ext} = Z_{int} + 2w_{thick}$, where w_{thick} is the external wall thickness; however, $X_{ext} = X_{int} + w_{thick}$ because the fully extended piston replaces one wall. The minimum internal floor-to-ceiling clearance Z_{clear} is limited by the underhang (w_{hang}) of the extrusion springs and the daughter device which is under construction, such that $Z_{clear} = Z_{int} - w_{hang}$. The desire to maintain adequate Y-axis clearance (w_{clear} on either side of daughter walls) between the extruding daughter device and the parental XZ walls requires that $Y_{int} = Z_{ext} + 2w_{clear}$. To ensure that the base of each Stewart platform manipulator is square with equal Y and Z dimensions, we require that $Z_{int} = (1/2) Y_{int}$.

The derivation of X_{int} is driven by the interplay of three design choices involving the piston, the elevator, and the Stewart platform manipulators.

First, for the fully retracted Stewart platform manipulator to allow adequate clearance, we require that: $X_{int} = x_{piston} + x_{pistonrod} + x_{throw} + x_{elevator} + x_{strutseg} + x_{chuck} + x_{back} + 2w_{extrusion} + Y_{ext} + w_{clear}$, where x_{piston} is the piston plate thickness, $x_{pistonrod}$ is the minimum extension of the piston rod between the piston and elevator, ($x_{pistonrod} + x_{throw}$) is the maximum extension of the piston rod between the piston and elevator, x_{throw} is the maximum possible piston throw during acoustic cycling between 1-4 atm driving pressure, $x_{elevator}$ is the elevator plate thickness, $x_{strutseg}$ is the length of each of the two (nested) strut segments comprising each strut of the Stewart platform manipulator, x_{chuck} is the height of the manipulator tool-holding chuck (excluding the length of various tool tips that might be grasped), x_{back} is the distance between the extrusion springs and the most retracted possible position of the end of the tool chuck (allowing adequate clearance for a grasped tool tip), and $w_{extrusion}$ is the width of the extrusion springs.

Second, for the fully extended Stewart platform manipulator to reach the materials transport wall with the end of the tool chuck, we require that: $x_{strutseg} + \alpha_{ext} x_{strutseg} + x_{chuck} = x_{screw} + 2w_{extrusion} + Y_{ext} + w_{clear}$, where α_{ext} is the maximum fractional extension of the second strut segment that extrudes from (and is the same length as) the first strut segment, and x_{screw} is the length of each of the four elevator drive screws.

Third, to prevent solvent entry into the assembler interior, the piston must completely cover all four lines of elevator drive screw holes in the inside hull wall face. This requires that: $x_{strutseg} + x_{chuck} + x_{back} = x_{piston} + x_{pistonrod} + x_{elevator} + x_{screw}$.

Combining these three design constraints on X_{int}, then solving for X_{int}, yields the following relation: $X_{int} = (Q_{scale} + (3 + \alpha_{ext}) Y_{ext}) / (1 + \alpha_{ext})$, where $Q_{scale} = (1 + \alpha_{ext}) x_{throw} + (1 - \alpha_{ext}) x_{screw} + (2 + 2 \alpha_{ext}) x_{back} + (2 \alpha_{ext}) x_{chuck} + (6 + 2 \alpha_{ext}) w_{extrusion} + (3 + \alpha_{ext}) w_{clear}$. Taking $w_{thick} = w_{hang} = w_{clear} = w_{extrusion} = x_{piston} = x_{elevator} = x_{chuck} = x_{back} = x_{screw} = 10$ nm, $x_{throw} = 15$ nm (Section B.4.2), and $\alpha_{ext} = 0.75$, then $x_{pistonrod} = 64.286$ nm, $x_{strutseg} = 74.286$ nm for the first strut segment alone (e.g., a fully contracted strut), $(1 + \alpha_{ext}) x_{strutseg} = 130.000$ nm for the fully extended Stewart platform two-segment strut, $Z_{clear} = 30$ nm minimum floor-to-ceiling clearance, and so:

$Z_{int} = 40$ nm $\quad Z_{ext} = 60$ nm
$Y_{int} = 80$ nm $\quad Y_{ext} = 100$ nm
$X_{int} = 323.572$ nm $\quad X_{ext} = 333.572$ nm
$V_{int} = 1{,}035{,}430.4\ nm^3$ $\quad V_{ext} = 2{,}001{,}432.0\ nm^3$
$S_{int} = 84{,}057.28\ nm^2$ $\quad S_{ext} = 118{,}743.04\ nm^2$

The density of the assembler is approximately $\rho_{assembler} = m_{assembler} / V_{ext} = 1895.9\ kg/m^3$, taking $m_{assembler} = 3.90826 \times 10^{-18}$ kg (Figure 4.42) and $V_{ext} = 2{,}061{,}432.0\ nm^3$ (Table 4.2). This is significantly denser than the solvent density ($\rho_{liquid} = 702.5\ kg/m^3$ for liquid n-octane), so in a $g = 9.81\ m/sec^2$ (1 g) gravity field the assembler will

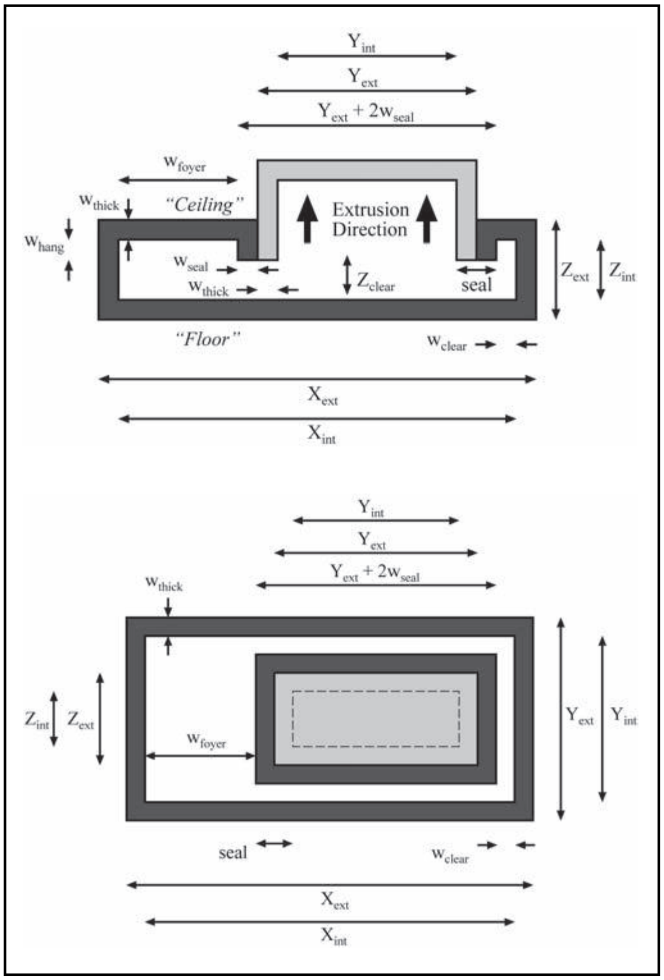


Figure B.1. Assembler wall dimensions: side view (above) and top view (below).

fall through the fluid from the top to the bottom of a reaction chamber of height $L_{chamber}$ = 2 microns in a time $t_{terminal} = L_{chamber} / v_{terminal}$ ~ 54 sec, where the particle terminal velocity $v_{terminal}$ is approximated by the Stokes sedimentation law[228] as $v_{terminal} = 2\ g\ L_{assembler}^2\ (\rho_{assembler} - \rho_{liquid})\ /\ 9\ \eta_{solvent}$ ~ 0.037 micron/sec, taking the mean assembler dimension $L_{assembler}$ ~ 100 nm and solvent absolute viscosity $\eta_{solvent}$ ~ 7.004×10^{-4} Pa-sec for n-octane at 273.15 K.[3116]

In keeping with the goal of design simplicity, the proposed molecular assembler is constructed almost exclusively of hydrocarbon and pure carbon structures, and all products the molecular assembler is capable of manufacturing are similarly restricted. The great majority of the atoms in the assembler reside in its outer shell, because the interior of the device is mostly (~86%) empty space. The walls consist of solid diamond with a carbon atom volume number density n_{carbon} ~ 176 atoms/nm^3 and all exposed surfaces are hydrogen terminated with a hydrogen atom surface number density of $n_{hydrogen}$ ~ 31.4 atoms/nm^2. Excluding external adsorbates, the exact total atom count in the shell is $N_{C,shell}$ (~ n_{carbon} $\{V_{ext} - V_{int}\}$) = 180,576,282 carbon atoms and $N_{H,shell}$ (~ $n_{hydrogen}$ $\{S_{ext} + S_{int} + S_{pistonsides}\}$) = 6,619,130 hydrogen atoms, where the hydrogen-terminated surface area around the piston plate at the end of its travel is $S_{pistonsides} = 2(2Y_{int} + 2Z_{int})\ (x_{piston})$ = 4,800 nm^2. There are additionally $N_{C,structure}$ = 14,654,725 carbon atoms and $N_{H,structure}$ = 2,058,676 hydrogen atoms in all non-shell internal structures (Table 4.2), giving a total whole-device carbon atom count of $N_{C,device}$ = 195,231,007 and a total whole-device hydrogen atom count of $N_{H,device}$ = 8,677,806. The device also includes exactly $N_{Si,device}$ = $N_{Sn,device}$ = 30 atoms each of silicon and tin in mechanosynthetic tool tips (though subsequent work[2322-2325] suggests replacing Si with Ge) for catalytic purposes which must be supplied by a very small number of vitamin molecules in the feedstock, giving an exact total atom count of N_{total} = 203,908,873 atoms in the proposed molecular assembler, as detailed in Table 4.2. Note that ~92% of all atoms reside in the hull wall and piston plate structures.

B.2 Some Limits to Assembler Scalability

This particular molecular assembler architecture may be scaled to larger or smaller sizes. There are, however, limits to the extent that the present architecture can be scaled without modification. Perhaps the most significant limit as size increases is the error rate. At some point, the assumption that a complete replication cycle can be completed with a modest probability of any error during the entire cycle will no longer be practical. The first concern would likely be the error rates in the relatively simple feedstock binding sites, which require feedstock that is, by present standards, very pure. As the total atom count in the design increases, and as a consequence the number of feedstock molecules that must by cycled through the intake mechanisms increases, the error rates of these mechanisms must be reduced. At some point, this would require adopting a more complex intake mechanism, adopting the strategies proposed by Drexler[208] (his Section 13.2.2) for a multi-staged cascade system that would be able to tolerate feedstock impurities while still delivering feedstock molecules to the assembler interior with a low overall probability of error.

With further increases in size, a point will be reached where radiation damage can no longer be neglected. Error detection and correction mechanisms would be required to insure correct system function. The current design assumes that the entire assembler can be discarded if a single error occurs — which is feasible only if the overall probability of an error is low. As size increases, the probability of a radiation-induced error will approach certainty, and the simple approach of discarding the entire assembler in the event of a single error will fail. While more sophisticated error isolation and correction strategies are feasible,[208,213] these lie outside the scope of the present analysis.

Another limit at even larger sizes in the scaling continuum is that the ratio of the surface area of the materials transport wall or the piston end wall to the volume of the device (or to the number of atoms per device) falls inversely with increasing linear dimension of the device (the Square-Cube law; Freitas,[228] p. 172). This makes it progressively more difficult for a sufficient quantity of power and materials to pass through the two YZ walls during a fixed replication time, thus limiting the ability to up-scale this specific architecture at significantly larger dimensions (though numerically the present design is far from these limits). The problem of feedstock bottleneck can be dealt with by increasing the input area exposed to the feedstock solution using "multiple thin sheets which have binding sites on their surfaces"[213] or by increasing the surface area of the intake by adopting a folded surface (Drexler,[208] Section 14.3.1.b) much as the gut has villi which greatly increase the surface area available for absorption of nutrients (Freitas,[228] Section 8.2.3). In this manner, convergent assembly could produce finished assemblies at least 1 m^3 in size[213] (Section 5.9.4).

At the smaller end of the scaling continuum, the probability of error in signal detection via the pistons that provide power and control scales[208] as ~exp(-L). This source of error increases rapidly in importance as device dimension L decreases, thus limiting our ability to downscale this design to significantly smaller dimensions. In addition, stiffness scales adversely with size, resulting in poorer ability to control positional uncertainty using smaller positional devices. While this source of error only increases linearly with smaller size, it will also limit scaling of the present architecture.

B.3 Gas Phase vs. Solvent Phase Manufacturing

One simple extruding-brick assembler environment would employ a two-component gas phase system — hydrocarbon feedstock molecules and vitamin molecules — with the assembler replicating in gaseous suspension. Diamondoid particles <4 microns in diameter that are suspended in gas at STP have a thermal velocity exceeding their terminal sedimentation velocity,[228] hence should not "settle out."

However, the importation of acoustic control signals having sufficiently high frequency and of acoustic energy pulses having sufficiently high intensity to power the assembler (Section B.4.2) is facilitated by liquid phase, rather than gas phase, operation, for several reasons.

First, a plane acoustic wave of initial amplitude P_0 (atm) and frequency ν traversing a uniform medium of thickness X and absorption coefficient α is partially absorbed during transit, with transmitted amplitude $P_x = P_0\ e^{-\alpha X}$. In the case of Ar gas atoms,[3117] which are incapable of either vibration or rotation, $\alpha_{Ar} = (1.7 \times 10^{-11}\ sec^2/m)\nu^2$ at 300 K and 1 atm, whereas for pure water $\alpha_{water} = (2.5 \times 10^{-14}\ sec^2/m)\nu^2$ and typically $\alpha_{organics} = (3\text{-}600 \times 10^{-14}\ sec^2/m)\nu^2$ for organic fluids near STP.[3118] However, in acetylene gas at 300 K and 1 atm pressure, the absorption coefficient as a function of frequency between 1-10 MHz peaks out[3117] as $\alpha_{acetylene} \sim (3\text{-}5 \times 10^{-4}\ sec/m)\nu$ — the vibrational relaxation time in acetylene gas at 300 K and 1 atm pressure, as measured by ultrasonic irradiation of the gas, is 7.4×10^{-8} sec, corresponding to ~13.5 MHz.[3117] For irradiation volumes having dimensions comparable to acoustic wavelength, e.g., X ~ 100 microns, absorption is far more severe in gas than in liquid. Absorption becomes less severe for shorter path lengths.

Second, the acoustic intensity I_{fluid} (W/m^2) that must be applied to a fluid to obtain a given planar acoustic wave pressure amplitude P_{fluid} is given by $I_{fluid} = P_{fluid}^2 / (2\ \rho_{fluid}\ v_{sound})$, where ρ_{fluid} is fluid density and v_{sound} is the speed of sound in the fluid.[228] For gaseous acetylene at STP, $\rho_{fluid} = 1.171$ kg/m^3 and $v_{sound} = 328$ m/sec as estimated from the Newton-Laplace equation for gases; for liquid n-octane at 20 °C and 1 atm, $\rho_{fluid} = 702.5$ kg/m^3 and the speed of sound in liquid n-octane at 20 °C is $v_{sound} \sim 1194$ m/sec.[3119] To produce a pressure amplitude of $P_{fluid} = 1$ atm within the fluid-filled reaction chamber, $I_{fluid} = 1.3 \times 10^7$ W/m^2 must be delivered to pure acetylene gas but only $I_{fluid} = 6.1 \times 10^3$ W/m^2 to pure liquid n-octane.

The thermal response to such power influx is readily, if crudely, estimated as follows. A power flux I_{fluid} crossing a reaction chamber of linear dimension $L_{chamber} \sim 2$ microns that is filled with fluid of thermal conductivity K_{fluid} and heat capacity C_V produces an equilibrium temperature differential of $\Delta T_{chamber} \sim I_{fluid}\ L_{chamber} / K_{fluid}$ in an equilibration time of $t_{EQ} \sim L_{chamber}^2\ C_V / K_{fluid}$.[228] For pure acetylene gas at STP, $K_{fluid} = 2.11 \times 10^{-2}$ W/m-K[3116] and $C_V \sim 1490$ J/m^3-K [3120], so inserting a 1 atm signal amplitude produces a decomposition-inducing temperature differential of $\Delta T_{chamber} \sim 1200$ K in an equilibration time $t_{EQ} \sim 0.28 \times 10^{-6}$ sec. For pure n-octane liquid at 20 °C and 1 atm, $K_{fluid} = 0.1292$ W/m-K[3116] and $C_V \sim 1.41 \times 10^6$ J/m^3-K[3121] (taking $C_P/C_V \sim 1.1$), so inserting a 1 atm signal amplitude produces an almost negligible $\Delta T_{chamber} \sim 0.1$ K in an equilibration time $t_{EQ} \sim 44 \times 10^{-6}$ sec.

A third important benefit of using a solvent is the significant elevation in the safe working pressure of highly sensitive carbon-rich feedstock molecules such as acetylene at room temperature — in the case of acetylene, from 2 atm as a pure gas to 17-20 atm as a gas dissolved in solvent (most commonly, acetone). This elevation applies as long as the acetylene remains in solution and does not effervesce or coalesce as micropockets of gas (e.g., during acoustic cavitation; Sections B.4.4.2 and B.4.4.3). A similar elevation of acetylene decomposition pressure threshold following solvation in liquid n-octane is anticipated but should be experimentally verified.

B.4 Acoustic Transducer for Power and Control

The proposed molecular assembler receives all power and control signals acoustically. Externally generated ultrasonic pressure waves travel through the solvent solution to the assembler device, whereupon a piston on the device is driven back and forth in a well-defined manner, passing energy and information simultaneously into the device.

Although an acoustically-actuated nanoscale piston has not yet been demonstrated experimentally, microfluidic actuators are well known[3122] and there are many reasons to expect that such small pistons will work as theory[208] predicts. For example, microscale pressure sensors have already been built using conventional MEMS fabrication techniques — e.g., a piezoresistive pressure microsensor diaphragm,[3123] a 250-micron medical pressure sensor that fits inside catheters,[3124] a 27-micron circular capacitive pressure sensor[3125] and an optical pressure sensor 7 microns thick.[3126] Micromachined flaps 45 microns in size have been raised from horizontal to vertical position by ultrasonic pulsing,[3127] demonstrating microscale acoustic actuation. Neutrophils ~8 microns in diameter that have phagocytosed a gas-filled microbubble exhibit large volume oscillations when insonated, with the trapped microbubbles experiencing viscous damping approximately sevenfold greater than for free microbubbles.[3128] HeLa cells acoustically irradiated at 1.5 MHz for 10 minutes lost microvilli and became smooth at 41.5 °C, but developed a heavily pitted and porous surface at 45 °C; careful monitoring suggested the damage was caused by bubble surface oscillations — that is, by acoustic energy transfer — not by collapse cavitation.[3129] Paclitaxel-carrying 2.9-micron lipospheres are "acoustically active," releasing drug when ultrasound irradiation induces surface oscillations of sufficient amplitude to rupture the artificial cell.[3130] Gas-filled 2-4 micron micropores insonated at 1-2 MHz may exhibit "pistonlike" or "membranelike" vibration modes.[3131-3133] At the nanoscale, pressure applied, then released, on carbon nanotubes causes fully reversible compression,[3134] and experiments have shown very low frictional resistance between nested nanotubes that are externally forced in and out like pistons.[3082] Masako Yudasaka, who studies C_{60} molecules trapped inside carbon nanotubes or "peapods" at NEC, expects that "the buckyball can act like a piston".[3135] Although microscale tympanic membranes appear absent in living systems, nanotube arrays are being investigated as directional acoustic sensors because these stereocilia-like structures are known to mechanically respond to acoustic energy.[3136-3138]

In this Section, we will look at the choice of acoustic frequency (Section B.4.1), the physical description of the acoustic transducer and pressure bands (Section B.4.2), piston fluid flow dynamics (Section B.4.3), thermal expansion, acoustic cavitation and resonance (Section B.4.4), and finally the energy efficiency and energy cost of molecular manufacturing using the proposed molecular assembler device (Section B.4.5).

B.4.1 Selection of Acoustic Frequency

Power and control signals are imported into the molecular assembler via externally generated high frequency acoustic signals. The need to provide sufficient coupling to the onboard transducer at reasonable power intensities dictates liquid phase, rather than gas phase, operations. Choice of frequency in liquid phase is driven by several offsetting considerations.

On the one hand, the highest feasible frequencies are preferred because they permit control information to be imported at the fastest possible rate, thus minimizing replication time for a design requiring a particular number of steps for its manufacture. Also, at higher acoustic frequencies the onset of harmful cavitation requires higher power intensities than are likely to be necessary for normal manufacturing operations (Section B.4.4).

On the other hand, operating frequency must not be too high for several reasons. First, attenuation of acoustic signals increases exponentially with frequency — operation at 100 MHz could allow significant attenuation in organic solvent (Section B.3), producing substantial solvent heating, unless path lengths are very short. Second, acoustic signals must be transduced by pistons whose drag losses are proportional to the square of the speed of sliding interfaces.[208] A 10 MHz piston that must travel ~10 nm/cycle moves at 0.1 m/sec dissipating a negligible ~0.001 kT/cycle, but at 100 MHz would move at 1 m/sec, a speed which can dissipate ~100 times more energy, up to ~0.1 kT/cycle (a significant loss) in sliding interfaces of these nanoscale dimensions.[208] Third, the piston must be operated slowly enough (<<100 MHz) to remain in the viscous regime while displacing solvent molecules adsorbed at the piston cavity walls during each cycle of piston operation (Section B.4.3.3.4). Fourth, the time required for feedstock molecule binding at the acetylene binding site to occur with a high enough probability ($q_{binding} = 1 - 10^{-12}$) to ensure full-cycle device replication with 99.99% certainty is $t_{binding} = 92 \times 10^{-9}$ sec, defining a maximum possible acetylene molecule import rate of ~11 MHz.

Acetylene (ethyne), the simplest alkyne and our carbon source in this design, can be used safely in the laboratory at atmospheric pressure without risk of flash decomposition up to 1000 K,[3139] though some decomposition in inert porcelain tubes is detected above 750 K.[3140] At room temperature, pure acetylene gas decomposes by deflagration above 2 atm and can detonate above 3.2 atm.[3141] (Deflagration is a slow-moving decomposition to the elements, producing fine carbon particles in the gas and gradual warming the tank as -54.34 kcal/mole heat of formation is slowly released, sometimes taking up to an hour before final detonation occurs.) Pure acetylene is shock sensitive and unlawful to ship under U.S. Department of Transportation regulations, but the gas dissolves readily in acetone, benzene, and other organic solvents; shipped as an acetone solution impregnating a porous solid inside the tank, C_2H_2 can safely tolerate pressures up to 17-20 atm before decomposition ensues. While butadiyne readily polymerizes in 7.4% acetone solution at room temperature during storage[3142] or topochemically when heated or irradiated,[3143] acetylene does not polymerize under similar conditions and requires either chemical catalysis,[3144] IR laser irradiation at 10^7-10^8 W/m^2,[3145] or diamond-anvil compression into the solid state at >3-4 GPa at room temperature for tens of hours[3146-3149] for polymerization to occur. Thus for the present design, we choose acetylene as our hydrocarbon feedstock molecule.

Can acetylene tolerate without decomposition the passage of MHz acoustic pulses that will carry power and control signals to the proposed molecular assembler? Although acetylene is shock sensitive, Wang and Springer[3117] have irradiated acetylene gas pressurized to 0.05-1 atm and heated to 300-900 K with 0.5-1 MHz ultrasound having a pulse duration of 20 μsec without observing any decomposition reactions. Hart et al[3150] observed sonolytic pyrolysis of acetylene in aqueous solution* at 20,000 W/m^2 and 1 MHz, but peak pyrolytic activity occurred at a solution concentration of 0.002 M C_2H_2, falling essentially to zero for more concentrated solutions >0.01 M such as we are proposing to use. Sonolysis of liquid decane at 20 KHz and at acoustic intensities up to ~10^6 W/m^2 evolves large amounts of C_2H_2,[3151] along with sonoluminescence,[3152] but there is no evidence of further decomposition of the acetylene. At the pressures (1-3 atm), frequencies (up to 10 MHz), C_2H_2 concentrations (0.15 M), and intensities (~6100 W/m^2) contemplated here, solvated acetylene should be equally ultrasound-tolerant and cavitation (Section B.4.4.3) resistant, an expectation that should be verified experimentally up to acoustic frequencies of at least 10 MHz.

These considerations, along with past analyses by others,[208,217] lead us to adopt $\nu_{acoustic} = 10$ MHz as a compromise operating frequency for the present design.

B.4.2 Physical Description of Acoustic Transducer and Pressure Bands

Our proposed molecular assembler employs a single large acoustic transducer at the piston end wall. The transducer consists of three simple components: (1) a piston plate, (2) a piston rod, and (3) a piston spring.

The **piston plate** is a hydrogen-terminated diamond block measuring $x_{piston} = 10$ nm thick and with square cross-section of dimension Y_{int} Z_{int}, less four small square corner cutouts of dimension $x_{vdWlegwidth}{}^2 = 100$ nm^2 each to accommodate the legs of the van der Waals cage (Section 4.11.3.4 (11)). Hence the piston plate area is $S_{transducer} = Y_{int}\,Z_{int} - 4x_{vdWlegwidth}{}^2 = 2800$ nm^2. The piston plate slides in contact (and makes a tight seal) with the hydrogen-terminated diamond inner hull walls and extended legs of the van der Waals cage that projects outward from the piston end wall at the hull corners. The piston end wall includes four small inward-pointing 1-nm tabs on the hull to prevent the piston plate from exiting the assembler, should the external pressure ever fall below 1 atm (e.g., during storage between replication cycles).

The **piston rod** attached to the center of the inside face of the piston plate that extends back through the elevator plate to engage the control chain mechanism that is attached to the other side of the elevator plate, in the assembler interior. The piston rod is a hydrogen-terminated diamond rectangular solid rod measuring $x_{rodwidth}{}^2$ in cross-section and $x_{rodlength} = x_{pistonrod} + x_{throw} + x_{elevator} + x_{elevatorrod} = 100$ nm in length, where $x_{rodwidth} = 4$ nm, $x_{pistonrod} = 64.286$ nm, $x_{throw} = 15$ nm and $x_{elevator} = 10$ nm, and $x_{elevatorrod} = 10.714$ nm, the minimum distance the piston rod protrudes beyond the inwardmost face of the elevator plate. (The maximum protrusion above the elevator plate is $x_{throw} + x_{elevatorrod} = 25.714$ nm.)

** Pyrolysis of acetylene[3150] occurred in a 60 ml reaction vessel containing 37.5 ml of solution and 22.5 ml of argon gas, with acetylene added to this gas in varying small amounts. Sonolysis of acetylene has the character of combustion, producing a large number of reaction products including H_2, CO, CH_4, various hydrocarbons with intermediate C atom numbers (predominantly with even C numbers rather than odd) such as benzene and various C_6H_6 isomers, high C number products such as naphthalene, and a yellowish soot consisting of particles of which 50% were >0.45 micron in size. At the peak rate, all acetylene was consumed in a few minutes of run time. The combustion mechanism is thought to involve a gas nucleus in the liquid that grows slowly and isothermally in the ultrasonic field. The mechanism of growth is rectified diffusion[3153] as the bubble oscillates. When the bubble reaches ~5 microns in size (at 1 MHz, in water), it undergoes a rapid adiabatic compression or collapse, momentarily creating temperatures of several thousand kelvins with pressures up to 100 atm. In contrast, a resonance bubble in n-octane at 10 MHz would be ~0.4 microns in diameter (Section B.4.4.3), larger than the assembler device and a substantial fraction of the ~2 micron reaction chamber width. Since the assembler solvent bath is an ultrapure liquid with no nucleation sites, and since the acoustic wavelength in n-octane at 10 MHz is ~100 microns >> 2-micron reaction chamber width (suggesting isotropic pressure throughout the chamber), cavitation bubbles should be difficult to initiate.*

Additionally, pyrolytic activity of the acetylene appeared to depend upon the presence of the water, which supplied H and O for various reaction pathways, but more importantly upon the presence of the argon, which (when dissolved in water) readily produces cavitation bubbles, creating a gaseous reaction microvessel wherein acetylene sonolysis can occur. At low acetylene concentrations, the rate of pyrolysis increases with C_2H_2 concentration. But at higher acetylene concentrations, due to the lower specific heat of acetylene as compared to argon, the temperature reached in the adiabatic compression of the bubble becomes lower with increasing hydrocarbon content, leading to a maximum in the yield vs. hydrocarbon concentration curve. At C_2H_2 concentrations exceeding 0.01 M, the temperatures achieved inside the cavitation bubble apparently are insufficient to induce sonolytic pyrolysis. The assembler feedstock solvent bath is anticipated to be a 0.15 M solution of acetylene.

In normal operation, the assembler resides in a pressurized fluid environment. At the beginning of the replicative cycle, pressure is slowly raised to 4 atm to unlock and activate any new daughter devices that may be present. The pressure is then slowly lowered to the baseline pressure of 2.0 atm. Thereafter, fluid pressure is varied between P_{min} = 1.0 atm and P_{max} = 3.0 atm in two pressure bands, each band 1.0 atm wide. (The acetylene decomposition pressure in n-octane solvent is assumed to be 17 atm (Section B.4.1), which lies comfortably above P_{max}.)

The **piston spring** is attached to the underside of the elevator plate at one end and to the piston rod at the other end. The spring ensures that the piston plate is at zero throw at ≤1 atm applied pressure, 5 nm throw at 2 atm, 10 nm throw at 3 atm, and 15 nm throw at ≥4 atm, and a 1-nm circumferential tab on the piston rod prevents its insertion more than 15 nm into the elevator plate, should the external pressure ever rise above 4 atm.

For any given control pulse, the probability q_{err} that the difference between two forces ΔF imposed on a piston that moves a distance L along its throw during a power stroke cannot be reliably distinguished from thermal noise[208] is given by $q_{err} = \exp(-L\,\Delta F_{min} / 4\,kT)$. Taking $q_{err} = 10^{-15}$ to ensure a 99% probability of successful completion of a 10^{13}-pulse command sequence at T = 273.15 K, and $L = L_{control}$ = 5.00 nm for each piston control band, then a power stroke force of ΔF_{min} = 104 pN must be applied in the control band to ensure adequate discrimination of piston pulses from thermal noise, representing a required minimum acoustic control pulse energy of ΔE_{min} = 521 zJ (~138 kT).

During single-band operation, the Gibbs free energy per power stroke is $\Delta G_{piston} = \Delta P_{piston} \Delta V_{piston}$, where the pressure change across the control band is $\Delta P_{piston} = \Delta P_{control} = 1.013 \times 10^5$ N/m^2 (1 atm) and the change in piston volume across the control band is $\Delta V_{piston} = \Delta V_{control} = L_{control}\, S_{transducer}$ = 14,000 nm^3. This confirms that $\Delta G_{piston} = \Delta G_{control} = \Delta P_{control}\, \Delta V_{control}$ = 1418 zJ (~376 kT per single-band power stroke) > ΔE_{min} and that the power stroke force of $\Delta F_{piston} = \Delta F_{control} = \Delta G_{control} / L_{control}$ = 284 pN > ΔF_{min} = 104 pN. The required piston spring constant is $k_{pistonspring} = \Delta F_{control} / L_{control}$ = 0.0567 N/m (56.7 pN/nm). An excursion by the piston across a control band (5 nm of travel) in one half-cycle at $\nu_{acoustic}$ = 10 MHz gives a mean piston sliding speed of v_{piston} = 0.1 m/sec. The total power supplied to the device during single-band operation is therefore $p_{assembler} = \Delta F_{control}\, v_{piston} / 2$ = 14.2 pW continuous, including the unpowered return stroke.

During double-band operation, we have $\Delta P_{piston} = 2\Delta P_{control} = 2.026 \times 10^5$ N/m^2 (2 atm), $L_{piston} = 2L_{control}$ = 10.00 nm, $\Delta V_{piston} = 2\Delta V_{control}$ = 28,000 nm^3, hence $\Delta G_{piston} = 4\Delta G_{control}$ = 5673 zJ (~1503 kT per double-band piston stroke), piston force $\Delta F_{piston} = 2\Delta F_{control}$ = 568 pN, and mean piston sliding speed v_{piston} = 0.2 m/sec at 10 MHz. Hence the total power supplied to the device during double-band operation is $p_{assembler} = \Delta F_{piston}\, v_{piston} / 2$ = 56.8 pW continuous, including the unpowered return stroke.

The acoustic waveform used to drive the acoustic transducer is a 10 MHz sine wave of amplitude 1-2 atm or 2-3 atm in single-band operation, or 1-3 atm in double-band operation, depending upon which control response is desired. Reddy et al[3154] describe an AT-cut planar quartz crystal 160 microns thick that is driven in the thickness-shear-wave mode to produce 10 MHz (fundamental resonance frequency) longitudinal pressure waves in liquid n-octane or in liquid water. Unlike the square waves illustrated in Figure B.2, pure sine waves have no higher-frequency components. However, a transition from a sine wave of one amplitude to a sine wave of another amplitude, or a transition between a flat pressure regime and a sinusoidally varying pressure regime, can generate higher-frequency acoustic components that must be accounted for. In a practical system, the piston only sees the top portions of each sinusoidal pulse because the mechanism has a minimum pressure threshold for response, in excess of thermal noise.

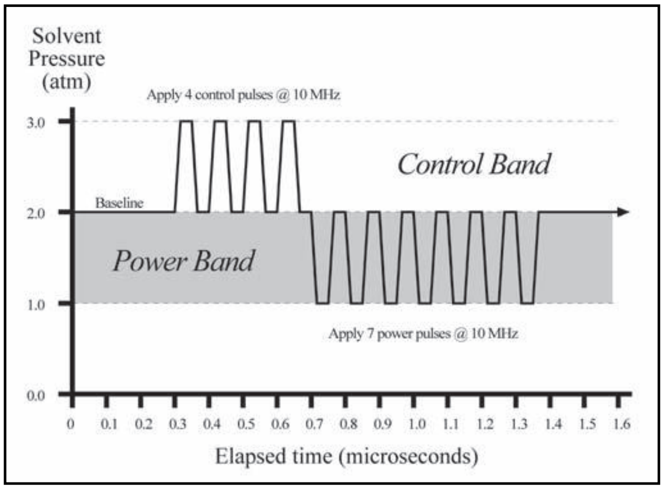


Figure B.2. Pressure bands for power and control (Merkle-Freitas molecular assembler uses a sine waveform, not the square waveform illustrated here).

B.4.3 Piston Fluid Flow Dynamics

A nanoscale piston being driven through viscous fluid experiences two kinds of effects. First, it feels the resistance to flow associated with bulk fluid flows (Section B.4.3.1). Second, it encounters wall-effect forces that are unique to the nanoscale (Section B.4.3.2). Section B.4.3.3 includes some further brief discussion of piston interactions with physisorbed solvent molecules at the wall-fluid interface.

B.4.3.1 Bulk Fluid and Laminar Flows

As the piston plate is pushed into the molecular assembler with increasing solvent liquid pressure, fluid flows into the volume vacated by the piston, approximating fluid flow through a tube. In such situations, classical continuum models assume, among other things, that the molecular graininess of the fluid can be ignored. This assumption fails when tube dimensions — say, tube radius R_{tube} — become comparable to or smaller than the characteristic molecular length scale (λ_{fluid}) of the fluid.[208] In a liquid, λ_{fluid} approximates the molecular radius; for n-octane molecules, λ_{fluid} ~ 0.3 nm. Taking $\pi R_{tube}^2 \sim S_{transducer}$, then R_{tube} (~ 29.85 nm) >> λ_{fluid} (~ 0.3 nm), so the classical continuum equations should well approximate the bulk fluid flows into the piston cavity as the piston is pushed into the assembler device by rising pressure. It is generally accepted that bulk liquid behavior exists more than ~5-10 molecular diameters (~2.5-5 nm for octane) from surfaces,[3155,3187] and molecular dynamics simulations of liquid-filled pores show that the average diffusion coefficient in the center of the pore approaches the bulk value at a distance of more than 10 molecular diameters from the pore's surface.[3202]

Continuum flow[3156] is typically governed by the well-known Hagen-Poiseuille Law (or more commonly, Poiseuille's Law), derived from the Navier-Stokes equations, which states that a pressure difference of ΔP_{fluid} between the ends of a rigid tube of radius R_{tube} and length L_{tube} will drive an aliquot of incompressible fluid of absolute viscosity η_{fluid} in laminar flow through the entire tube length in a time $t_{flow} = 8\, \eta_{fluid}\, L_{tube}^2 / R_{tube}^2\, \Delta P_{fluid}$. Taking $\eta_{fluid} = 5.40 \times 10^{-4}$ Pa-sec for n-octane,[3116] R_{tube} ~ 29.85 nm, L_{tube} = 10 nm (double-band operation, the longest piston throw under normal conditions), and $\Delta P_{fluid} = 2.026 \times 10^5$ N/m^2 (2 atm), then

$t_{flow} = 2.39 \times 10^{-9}$ sec, an implied maximum cycling frequency of 418 MHz. However, the actual piston is only operated at $\nu_{acoustic} = 10$ MHz, so the n-octane fluid molecules have plenty of time to enter the piston cavity, in near-perfect laminar flow (see below) and in equilibrium. In this regime, the drag power dissipation can be crudely estimated from Stokes' law which gives the drag power for a sphere of radius R moving through a fluid of viscosity η at velocity v as $p_{Stokes} = 6 \pi \eta R v^2 \sim 12$ pW $<<$ $p_{assembler} = 56.8$ pW during double-band operation (Section B.4.2), taking $R = R_{tube}$, $\eta = \eta_{fluid}$ for n-octane, and $v = v_{piston} \sim (2 L_{tube} \nu_{acoustic}) = 0.2$ m/sec during a double-band cycle of fluid flow. The equivalent drag force is $F_{Stokes} = p_{Stokes} / v \sim 60$ pN $<< \Delta F_{piston} = 568$ pN for double-band operation (Section B.4.2). During single-band operation, $v_{piston} \sim 0.1$ m/sec so the Stokes law drag power is $p_{Stokes} \sim 3$ pW $<< p_{assembler} = 14.2$ pW (Section B.4.2). The equivalent drag force is $F_{Stokes} \sim 30$ pN $<< \Delta F_{piston} = 284$ pN for single-band operation (Section B.4.2).

The resistance to Poiseuille (laminar) flow in a pipe is the minimum of resistance of all possible flows in a pipe.[3157] If the flow becomes turbulent, the resistance increases. The determinative parameter is a dimensionless quantity called the Reynolds number,[3158-3160] N_R, which is the ratio of the inertial pressure ($\sim \rho v^2$) to the viscous pressure ($\sim \eta v / R$) in the flow of a fluid of density ρ, or, for our piston system, $N_R = \rho_{fluid} v_{piston} L_{char} / \eta_{fluid} = 0.001$, taking $\rho_{fluid} = 702.5$ kg/m^3 for n-octane[3161] and $v_{piston} \sim 0.2$ m/sec during a double-band cycle of fluid flow. The characteristic linear dimension L_{char} is the ratio of the volume of the fluid to the surface area of the walls that bound it,[3160] giving $L_{char} = 4.12$ nm for our piston during a double-band cycle. A Reynolds number this low indicates that bulk-phase fluid flow will be extremely laminar, both into and out of the piston cavity, and highly uniaxial, with the entire fluid moving parallel to the local orientation of the walls.[3160]

Classical Poiseuille flow is characterized by a parabolic velocity profile over the cross-section of the channel. However, it is unlikely that the flow of octane-solvated acetylene into the piston cavity will be able to develop a parabolic velocity profile across the flow channel (most favored for cavity aspect ratios[3162] near 1:1, as here). Brody and Yager[3162] estimate that small solute molecules of a size similar to the solvent molecules will have a relatively large diffusion coefficient, hence will move with a plug flow (~constant velocity) profile whenever $N_R < 0.001$ — very close to our estimated $N_R = 0.001$. Additionally, when fluid enters a narrow channel from a wider one, the flow profile is not immediately parabolic.[3163] For low Reynolds number fluid flow, the inlet distance for flow to become 99% fully developed is $\sim R_{tube}$, but since R_{tube} (= 29.85 nm) > L_{tube} (= 10 nm) there is insufficient length even in the longest possible piston throw to allow the flow to become fully developed. These factors argue for plug flow inside the piston cavity.

In general, a large Reynolds number implies a preponderant inertial effect and the onset of turbulence; a small Reynolds number implies a predominant shear effect (e.g., viscosity) and the maintenance of laminar flow, with no-slip conditions (i.e., no fluid flow at the surface of an object[3164]). Reynolds[3158] found that the transition from laminar to turbulent flow typically occurs at $N_R > 2000$-13,000, depending upon the smoothness of the entry conditions. The lowest transitional value obtainable experimentally on a rough entrance in macroscale channels was $N_R \sim 2000$, although when extreme care was taken to establish smooth entry conditions the transition could be delayed to Reynolds numbers as high as 40,000. Recent studies of Reynolds numbers in microfluidics flow systems confirm transitional values of $N_R > 100$ for the onset of turbulence, and maintenance of laminar flow as long as the "switching time" τ_{switch} on which the pressure driving the flow varies (e.g., $\sim 10^{-7}$ sec at 10 MHz) is longer than the characteristic time $\tau_{char} = \rho_{fluid} R_{tube}^2 / \eta_{fluid}$ ($\sim 10^{-9}$ sec for our assembler piston)[3162] — such pressure changes may be considered quasi-static. The Stokes drag law used earlier should remain applicable as long as flow remains laminar.

Laminar flows in nanoscale channels are well-known in biology. For example, cellular and nuclear microinjection through fine glass pipette tips as small as 200 nm in diameter is commonplace in the experimental biological sciences,[3165] and the syringelike T4 bacteriophage ejects ~200,000 nm^3 of DNA material through a 2.5-nm diameter hollow core protein nanotube at a flow velocity as high as 0.36 mm/sec, forced by a ~30 atm head pressure.[1758-1762] Molecular dynamics simulations of fluid flow inside 1.3-1.6 nm diameter single-walled carbon nanotubes have also been reported.[3166,3167]

B.4.3.2 Confined-Fluid Density Layering Due to Near-Wall Solvation Forces

Despite laminar bulk-fluid flows throughout the center regions of the piston cavity, nanoscale density layering near the liquid-solid interface is a universal feature of liquids[3232] which has been demonstrated experimentally[3190,3191,3194] and in many simulations.[3173-3177] Layering is observed both in long chain fluids and in fluids of spherical molecules, and even in simulations of hard particles against hard walls.[3168] Layering is caused by the packing of molecules against the surface, which is partly an entropic effect due to the increase of free volume of individual molecules when the density is layered compared to that in a uniform density.[3232]

The variations in density are most significant for fluids confined in very narrow spaces. It is believed that solvation forces are a signature of molecular ordering induced by the confining surfaces.[3169] In general,[3194] low molecular weight fluids flowing between two walls separated by more than 5-10 molecular diameters (~2.5-5 nm for n-octane) experience a monotonically attractive van der Waals force as expected from continuum theories. But at smaller separations the force generally oscillates with distance, varying between attraction and repulsion, with a periodicity equal to the mean diameter of the liquid molecules. The oscillatory force law is a reflection of the tendency of simple molecules to order in layers near a smooth solid surface, and the enhancement of this ordering when two surfaces are in close proximity.[3194] Simulation studies have shown that symmetric molecules are absorbed into or squeezed out of the confined space in a stepwise fashion,[3169] i.e., on a whole-layer basis,[3180-3185] when the surface separation is changed. The confined film can undergo a series of pseudophase transitions between solidlike and liquidlike configurations.[3184-3187]

Solvation force-driven density oscillations in confined liquids have been demonstrated for n-octane and related isomers in both theoretical[3175-3180] and experimental[3155,3192-3194] studies, for non-octane alkanes both theoretically[3170-3172, 3185] and experimentally,[3178,3193-3200] and for various octane mixtures such as octane-butane,[3232] octane-methanol,[3155] or octane-water.[3155,3193] The self-diffusion coefficient within the layers (which is related to the effective viscosity) has been shown[3204-3207] to drop abruptly when films of spherical molecules are confined below a given critical film thickness, indicating a rather sharp solidification process. Interestingly, octane shows among the fewest number of density oscillations (typically just two layers[3173,3192-3194]) with distance from the confining surface, before resuming bulk density, of the common alkanes.

However, the space between adjacent walls in the piston cavity is $\sim Z_{int} = 40$ nm $>> 2.5$-5.0 nm = 5-10 molecular diameters of the n-octane molecule. It has been found[3155] that liquid n-octane confined experimentally between two mica surfaces exhibits liquid behavior for gap thickness >5 molecular layers, and solidlike behavior for <5 molecular layers. In general, when two surfaces are farther apart than ~10 molecular diameters, a simple fluid in the gap retains its bulk Newtonian behavior and the shear plane remains coincident with the physical solid-liquid interface to within ~1 molecular diameter at shear rates up to 10^5 sec^{-1},[3208-3211] and with no change in thin-film viscosity from the bulk liquid for long-chain linear alkanes such as tetracosane ($C_{24}H_{50}$) for strain rates up to 10^8-10^{11} sec^{-1}.[3214] While fluid strain rates found in a number of practical applications such as the lubrication of disk drives, micromachines, and camshaft lifters in automobile engines[3215] can reach ~10^8 sec^{-1}, the shear rate inside our assembler piston cavity can only reach a maximum of ~v_{piston} / Z_{int} = 50 x 10^5 sec^{-1} for v_{piston} = 0.2 m/sec in double-band operation.

Surface force balances have also been used to probe the dynamic and structural properties of ultrathin films and suggest that, even when confined, liquids retain their bulk viscosity as long as the films are thicker than about ten molecular diameters, right up to the liquid-confining/solid interface (to within a single molecular layer).[3210-3213] As Klein and Kumacheva[3203] explain: "The picture that emerges is that, as the [confining] surfaces approach each other from large separations, the confined liquids retain their bulk fluidity across the entire gap, until at a critical spacing the entire film undergoes a liquid-to-solid transition."

For unconfined bulk liquids in contact with a single smooth solid surface, some layering of the molecules is induced, decaying over a few molecular diameters from the surface.[3201-3204] This layering is due to simple geometric packing. But theoretical molecular dynamics and Monte Carlo studies of liquid films of n-octane,[3173,3232] decane,[3169] and hexadecane[3216] on various isolated surfaces near room temperature, and related experimental work,[3210-3212] have confirmed that bulk simple liquid alkanes near a surface remain fluid right up to the solid-liquid interface.

The conclusion is that bulk viscosity flow conditions should prevail across the entire width of the piston chamber, except for piston interactions with physisorbed solvent molecules at the wall-fluid interface which is the subject of the following Section.

B.4.3.3 Piston Operation in the Desorption and Viscous Regimes

A rectangular hydrogen-terminated diamond piston plate moves back and forth inside a cavity whose walls also consist of hydrogen-terminated diamond. The outward-facing surface of the piston plate and the inward-facing surfaces of the piston cavity are exposed directly to the external solvent environment. A molecular dynamics simulation of hexadecane wetting the Au(001) surface at 315 K shows that the initial monolayer is complete in ~1 x 10^{-9} sec;[3217] another simulation study of liquid octane near a waxy interface required ~0.4 x 10^{-9} sec for monolayer adsorption equilibration,[3232] and equilibration times of 0.3-1 x 10^{-9} sec are typical in alkane film adsorption or confined liquid studies.[3185] For our assembler design, we assume that predominantly n-octane molecules physisorb to the passivated diamond walls in a time t_{adsorb} ~ 1 x 10^{-9} sec << t_{piston} = $(2\ \nu_{piston})^{-1}$ = 50 x 10^{-9} sec. Hence, throughout each return stroke of the piston (wherein the cavity is reduced to zero volume), all cavity walls that are still exposed to solvent should be reliably coated with a complete physisorbed monolayer of n-octane molecules.

B.4.3.3.1 Nature of the Physisorbed Monolayer

Although n-octane molecules exhibit numerous vibrational modes and surface conformations on diamond,[3218, 3219] experiments and molecular dynamics simulations have shown that an n-octane monolayer deposited on hydrogen-terminated diamond C(111):H(1x1),[3220] simulated hydrocarbon-like waxy substrate,[3232] hydroxylated α-Al_2O_3(0001),[1109] Cu(111),[3221,3222] Cu(100),[3222] or Au[3223] surfaces adsorbs octane molecules with their C-C-C plane oriented parallel to the substrate. Other studies[3224-3230] have confirmed that for straight chain molecules such as the n-alkanes and for various linear polymer melt molecules, the molecules align parallel to the solid surfaces. A surface monolayer of n-octane on diamond has an areal density of a_{octane} ~ 0.60 nm^2/molecule[3231] and a thickness of $\delta_{monolayer}$ ~ 0.3-0.6 nm.[3173,3180,3194,3232-3234] A molecular dynamics study by Gupta, Koopman, et al[3173,3176] of liquid n-octane at 360.6 K physisorbed on a planar fcc surface having a solid-liquid adhesive energy parameter equivalent to the basal plane of graphite found that the population of octane molecules nearest the surface showed only 36% of adsorbed molecules with 8 hydrogen-surface contacts, 22% with 5-7 contacts, and 42% with 1-4 contacts, and rotational relaxation times of order ~0.01 nanosec.

Consistent with related studies,[3187-3189] we assume that van der Waals physisorption by n-octane induces no reconstruction of the underlying hydrogen-terminated diamond wall surface structure.

B.4.3.3.2 Operational Regimes Defined

The interaction of the piston plate with the physisorbed n-octane monolayer during the piston return stroke will be governed by the characteristic diffusion time $\tau_{diffusion||}$ of the adsorbed n-octane molecules parallel to the surface. According to the well-known Einstein-Smoluchowski diffusion equation,[228] $\tau_{diffusion||}$ ~ $(\Delta x)^2$ / (2 $D_{diffusion||}$) where Δx is the distance diffused in a fluid having lateral diffusion constant $D_{diffusion||}$. For an adsorbed monolayer, Δx may be taken as the mean intermolecular separation distance within the monolayer, or Δx ~ $a_{octane}{}^{1/2}$ ~ 0.77 nm for n-octane. $\tau_{diffusion||}$ is thus the mean time for a physisorbed molecule to diffuse one intermolecular separation distance. Although no studies of any kind have been done on the physisorption of n-octane on diamond surfaces, estimates from molecular dynamics and other theoretical investigations have found, for example, that $D_{diffusion||}$ ~ 0.57 x 10^{-9} m^2/sec for 1.3 monolayers coverage of liquid n-octane physisorbed on α-Al_2O_3(0001) at 300 K,[3234] $D_{diffusion||}$ ~ 7.5 x 10^{-9} m^2/sec for an n-octane monolayer on Cu(111) surface at 200 K,[3235] $D_{diffusion||}$ ~ 1.7 x 10^{-9} m^2/sec for butane at 149 K or hexane at 215 K adsorbed on graphite,[3236] $D_{diffusion||}$ ~ 2.1 x 10^{-9} m^2/sec for butane at 150 K on Pt(111) at close to monolayer coverage,[3237] $D_{diffusion||}$ ~ 10 x 10^{-9} m^2/sec for 1.0 monolayer coverage of liquid benzene on the basal plane of graphite at 250 K,[3238] and $D_{diffusion||}$ ~ 2.8 x 10^{-9} m^2/sec for the translational self-diffusion coefficient for liquid ethylene adsorbed on the basal plane of graphite at 75 K.[3239] Conservatively taking $D_{diffusion||}$ ~ 1.0 x 10^{-9} m^2/sec for liquid octane adsorbed on hydrogen terminated diamond at 300 K, then $\tau_{diffusion||}$ ~ 0.3 x 10^{-9} sec.

The characteristic time required for the piston plate to travel one intermolecular separation distance (Δx) is τ_{piston} = Δx / v_{piston}. This defines three distinct operating regimes for the piston relative to the surface-adsorbed n-octane monolayer, as discussed further, below:

I. Desorption Regime: $\tau_{piston} << \tau_{diffusion||}$ (~ 0.3 x 10^{-9} sec)
II. Transitional Regime: τ_{piston} ~ $\tau_{diffusion||}$ (~ 0.3 x 10^{-9} sec)
III. Viscous Regime: $\tau_{piston} >> \tau_{diffusion||}$ (~ 0.3 x 10^{-9} sec)

B.4.3.3.3 Operation in the Desorption Regime

Assuming double-band piston operation for the rest of this discussion, the center of the transitional regime would occur at a piston frequency of $\nu_{transitional}$ ~ Δx / (2 L_{piston} $\tau_{diffusion||}$) ~ 128 MHz, taking L_{piston} = 10 nm (Section B.4.2). If the piston is operated above this frequency, then there is insufficient time for adsorbed molecules to laterally diffuse and escape from the approaching

Table B.1. Enthalpies of adsorption (desorption) for physisorption of even-numbered linear-chain hydrocarbons on various surfaces

Physisorbed Molecule	Physisorption Surface	Physisorption Enthalpy (zJ/molecule)	zJ per CH_x Unit	Ref/Type
ethane (C_2H_6)	graphite, 300 K	18.4	9.2	3241 C
ethane (C_2H_6)	graphite, 300 K	26.4-33.4	13.2-16.7	3242 E
ethane (C_2H_6)	graphite, 196 K	28.7	14.4	3241 E
ethane (C_2H_6)	graphite, 173 K	30	15	3243 E
ethane (C_2H_6)	graphite, 300 K	33.4	16.7	3242 C
ethane (C_2H_6)	graphite, 200-300 K	37.4	18.7	3244 C
n-butane (C_4H_{10})	graphite, 279-285 K	24-29	6-7.3	3245 C
n-butane (C_4H_{10})	α-Al_2O_3(0001), 100 K	43	11	3234 C
n-butane (C_4H_{10})	graphite, 300 K	55.6-57.0	13.9-14.2	3242 E
n-butane (C_4H_{10})	Pt(111)	57	14	3246 E
n-butane (C_4H_{10})	α-Al_2O_3(0001), 100-150 K	58	15	3247 E
n-hexane (C_6H_{14})	α-Al_2O_3(0001), 100-150 K	72.3	12	3247 E
n-octane (C_8H_{18})	graphite		0.8	3176 C
n-octane (C_8H_{18})	(heat of fusion)	34.4	4.3	2987 E
n-octane (C_8H_{18})	Au(001) @ 300 K		5	3176 C
n-octane (C_8H_{18})	mica @ 360.6 K		6-10	3176 C
n-octane (C_8H_{18})	Pt(111)	~70-80	8.8-10	3248 E
n-octane (C_8H_{18})	α-Al_2O_3(0001), 100/300 K	75	9.4	3234 C
n-octane (C_8H_{18})	mica, 300 K	100-170	12-21	3197 C
n-octane (C_8H_{18})	α-Al_2O_3(0001), 100-150 K	101.4	12.7	3247 E
n-decane ($C_{10}H_{22}$)	graphite, 291-293 K	69-76	7-8	3245 C
n-dodecane ($C_{12}H_{26}$)	mica	190-380	16-32	3174 C
n-tetradecane ($C_{14}H_{30}$)	graphite	259	18.5	3249 C
n-hexadecane ($C_{16}H_{34}$)	graphite @ 298 K	55	3.4	3250 E
n-hexadecane ($C_{16}H_{34}$)	cast iron @ 298 K	56	3.5	3251 E
n-hexadecane ($C_{16}H_{34}$)	Au(001), 350 K	111	7	3175 C
n-hexadecane ($C_{16}H_{34}$)	Au(100), 350 K	122-146	7.6-9.1	3216 C
n-$C_{20}H_{42}$	cast iron @ 298 K	75	3.8	3251 E
n-$C_{22}H_{46}$	graphite @ 298 K	98	4.5	3250 E
n-$C_{24}H_{50}$	cast iron @ 298 K	130	5.4	3251 E
n-$C_{28}H_{58}$	graphite @ 298 K	158	5.6	3250 E
n-$C_{28}H_{58}$	cast iron @ 298 K	186	6.6	3251 E
n-dotriacontane ($C_{32}H_{66}$)	MoS_2	55-85	1.7-2.7	3252 E
n-dotriacontane ($C_{32}H_{66}$)	WS_2	83-86	2.6-2.7	3252 E
n-dotriacontane ($C_{32}H_{66}$)	cast iron @ 298 K	238	7.4	3251 E
n-dotriacontane ($C_{32}H_{66}$)	graphite	240-350	7.5-10.9	3252 E

E = experimental value, C = calculated or estimated value, or result of computational simulation

piston plate, so the adsorbed molecules must be mechanically desorbed from the surface in order to allow the piston plate to pass.

Heat is evolved during the physical adsorption process,[2987] so energy must be added to molecules physisorbed on a surface in order to desorb them. A laterally-moving tight-seal scraping plate that applies a mechanical energy greater than the bulk material energy of adsorption (aka. energy of desorption, heat of adsorption or enthalpy of adsorption) to an n-octane molecule physisorbed on a diamond surface is likely to desorb that molecule from the surface. Table B.1 shows desorption energies for even-numbered linear-chain hydrocarbons on different surfaces, at various temperatures. Graphite is considered a very weakly physisorbing "nonwetting" surface for hydrocarbons, gold is a moderately physisorbing surface, and mica is a strongly physisorbing surface.[3173] According to polymer adsorption theory,[3240] adsorption or desorption from solution generally requires 0.2 kT to 4 kT per interacting polymer segment (e.g., ~0.8-17 zJ per carbon segment in a long-chain n-alkane at 300 K), depending on the chemistry of the repeat segments and of the solvent. Aside from one study[3189] of the physisorption of acetylene on the diamond (111) surface, the physical adsorption of alkanes and other hydrocarbons on diamond surfaces has yet to be systematically investigated. The range of desorption enthalpies appears to be 1-15 zJ per C unit for hydrocarbons on graphite and a few other hydrocarbon-nonwetting surfaces. In the absence of hard experimental data or reliable computational simulations, a value of ~1 kT/segment or ~4 zJ per CH_x unit for octane on diamond surface at 300 K appears reasonable, though the precise choice does not sensitively affect our conclusions.

Taking the enthalpy of desorption for physisorbed n-octane on diamond at 300 K as $E_{desorb} \sim 32$ zJ/molecule, then the power required for piston motion is $p_{desorb} \sim 4\ \nu_{piston}\ E_{desorb}\ (Y_{int} + Z_{int})\ L_{piston} / a_{octane}$. Taking $L_{piston} = 10$ nm, $Y_{int} = 80$ nm, $Z_{int} = 40$ nm, $a_{octane} \sim 0.60$ nm^2/molecule, and $\nu_{piston} > 128$ MHz, then $p_{desorb} > 33{,}000$ pW >> $p_{assembler}$ (= 56.8 pW; Section B.4.2), and so the piston becomes securely pinned by solvation forces and cannot move at this frequency.

B.4.3.3.4 Operation in the Viscous Regime

Again assuming double-band piston operation, a piston frequency of $\nu_{piston} = 10$ MHz << $\nu_{transitional} = 128$ MHz. Specifically, at 10 MHz, $\tau_{piston} = 3.85 \times 10^{-9}$ sec >> $\tau_{diffusion||}$ (~ 0.3×10^{-9} sec) and so the piston is found to be operating well into the viscous regime. When the piston is operated in the viscous regime, there is sufficient time for adsorbed molecules to laterally diffuse and escape from the approaching piston plate during the return stroke. As a result, the adsorbed molecules need not be mechanically desorbed from the surface in order to allow the piston plate to pass. Instead, the piston moves through the monolayer much like a solid object passing through a viscous fluid, and the drag power required for this motion can be crudely estimated from Stokes' law (Section B.4.3.1), as follows.

First, according to the Einstein-Stokes equation,[228] viscosity is inversely proportional to the diffusion coefficient. Since the self-diffusion constant $D_{bulk} \sim 2.9 \times 10^{-9}$ m^2/sec for bulk n-octane at 300 K,[3234] then the effective lateral viscosity of the adsorbed octane monolayer is $\eta_{monolayer} \sim \eta_{bulk}\ (D_{bulk} / D_{diffusion||}) \sim 1.57 \times 10^{-3}$ Pa-sec, taking $\eta_{bulk} = 5.40 \times 10^{-4}$ Pa-sec for bulk liquid n-octane[3116] and $D_{diffusion||} \sim 1.0 \times 10^{-9}$ m^2/sec for liquid octane adsorbed on hydrogen terminated diamond at 300 K (Section B.4.3.3.2). Second, the Stokes' law drag force and drag power are both proportional to area$^{1/2}$. Taking monolayer thickness $\delta_{monolayer} \sim 0.5$ nm (Section B.4.3.3.1), then the effective Stokes radius for the portion of the piston surface in contact with the monolayer is $R_{monolayer} \sim ((2Y_{int} + 2Z_{int})\ \delta_{monolayer} / \pi)^{1/2} = 6.2$ nm. Hence the additional Stokes' law drag power for the piston plate edge moving through the physisorbed n-octane monolayer at a viscous regime velocity $v_{piston} = 0.2$ m/sec is $p_{monolayer} \sim 6\,\pi\ \eta_{monolayer}\ R_{monolayer}\ v_{piston}{}^2 \sim 7.3$ pW << $p_{assembler}$ (= 56.8 pW; Section B.4.2), and so the piston moves easily through the monolayer (at low speeds) with only modest energy losses.

Note that while no-slip conditions at the walls are customarily assumed in analyses of low Reynolds number fluid flow regimes and Poiseuille flows,[3164] there are cases where this assumption does not hold.[3253] Most notably, one molecular dynamics study[3254] of simulated liquid-phase constant-temperature linear alkane chains confined between atomistic pure titanium walls under shear flow conditions (walls translating in opposite directions) found that the alkane chains exhibited a tendency for slip at the walls, as evidenced by a bifurcated density profile, by small discontinuities in the velocity and temperature profiles at the wall-fluid interface, and by higher mean-square end-to-end distance along the shear flow direction.

To summarize: During double-band operation, the gross acoustic power input to the piston is $p_{assembler} = 56.8$ pW (Section B.4.2), which, when reduced by the bulk drag loss of $p_{Stokes} \sim 12$ pW (Section B.4.3.1) and the monolayer drag loss of $p_{monolayer} \sim 7.3$ pW, gives a net acoustic power input delivered to the piston of $p_{piston} \sim 37.5$ pW and an available force $\Delta F_{piston} = 2\ p_{piston} / v_{piston} = 375$ pN during the power stroke. During single-band operation, the gross acoustic power input to the piston of $p_{assembler} = 14.2$ pW (Section B.4.2) is reduced by the bulk drag loss of $p_{Stokes} \sim 3$ pW (Section B.4.3.1) and the monolayer drag loss of $p_{monolayer} \sim 1.8$ pW, giving a net acoustic power input delivered to the piston of $p_{piston} \sim 9.4$ pW and an available force $\Delta F_{piston} = 2\ p_{piston} / v_{piston} = 188$ pN during the power stroke.

B.4.3.3.5 Physisorption and Desorption of Nonsolvent Molecules

Since there is one acetylene molecule for every ~59 n-octane molecules in the hydrocarbon feedstock solution, the possible physisorption of solvated acetylene molecules from the external solvent bath to the piston cavity passivated diamond walls must also be evaluated. Experiments[3189] on the physisorption of acetylene on the diamond C(111)-H(1x1) surface from gas phase show that the C_2H_2 molecule adsorbs nearly flat on terraces but is slightly tilted on defect sites, covering four surface hydrogens. This in-plane orientation of the acetylene monolayer is not unexpected because C_2H_2 has high π electron density around the C≡C triple bond, the most energetically favorable position to be attacked by hydrogen-containing species to form a hydrogen bond, and because electrostatic interactions also favor the horizontal orientation of C_2H_2 on the diamond surface.

Will n-octane or acetylene be preferentially adsorbed on the passivated diamond surface? In principle, the heat of adsorption is of the same order of magnitude as the heat evolved during phase changes such as freezing or condensation,[2987] since all these processes are governed by van der Waals interactions. The heat of fusion for n-octane at 1 atm is 34.4 zJ/molecule;[2987] for acetylene, the heat of fusion is only 4.17 zJ/molecule[3255] and 1.34 zJ/molecule for the heat of sublimation,[3256] which would appear to strongly favor the persistence of octane.

A molecular dynamics simulation by Xia and Landman[3217] found that in an equal-weight mixture of hexane and hexadecane on the Au(001) surface at 315 K, both species initially adsorb in the nearest-surface monolayer with a slight preference in number of attached segments for the shorter-chain hexane molecules. But the longer chain quickly crowds out the shorter chain by reptation motions, so that by 0.8×10^{-9} sec the attached segment counts are about equal and by 8×10^{-9} sec there are 20 times more hexadecanes than hexanes attached. Similarly, a simulation of an octane-butane mixture on a waxy surface at 223 K produced an early preferential adsorption of the butane in the layer nearest the surface, but the simulation was halted after only 0.2×10^{-9} sec so any subsequent possible substitution effects could not be observed.[3232] In a mixed-hydrocarbon solution of $C_{14}H_{30}$ in benzene on a graphite surface, alkane chains were found to rapidly penetrate the previously adsorbed benzene layers near the surface and adhere to the graphite.[3249] In one early study, n-alkanes with carbon numbers from 16-32 in n-heptane solution readily displaced the shorter-chain heptane and physisorbed to surfaces of cast iron, graphite, MoS_2 and WS_2.[3251,3252] This preferential adsorption of longer-chain hydrocarbons is believed to be driven by lateral intermolecular interactions within the adsorbed layer,[3250] rather than by adsorbate-substrate interaction, which suggests that the much larger n-octane molecules will adsorb to diamond in preference to acetylene molecules, leaving a weakly physisorbed close-packed n-octane monolayer at the surface with the carbon skeleton planes of the octane molecules oriented parallel to the surface,[3250] and relatively few surface-physisorbed acetylene molecules. The adsorption stability of the alkanes increases with increasing chain length.[3257]

Vitamin molecules are present in feedstock at the parts-per-million level and can be designed to minimize their physisorption to diamond walls, hence should not significantly contribute to piston drag forces or drag power losses. The authors would encourage a more comprehensive molecular dynamics analysis of nanoscale piston operations.

B.4.4 Thermal Expansion, Acoustic Cavitation and Resonance

The proposed molecular assembler, as an acoustically-driven device, dissipates energy locally, hence produces waste heat which could produce small stresses from uneven wall heating; this possibility is evaluated in Section B.4.4.1. Sections B.4.4.2-B.4.4.6 consider the possibility of acoustic cavitation, resonances, and related effects in a submicron-scale diamond box acoustically driven at 10 MHz in an n-octane bath. Studies of acoustic cavitation in liquid n-octane have yet to be performed and should be undertaken as soon as possible. The risks of cavitation in the nanomedical context have already been noted elsewhere.[228]

B.4.4.1 Thermal Expansion in Diamond Walls

The proposed molecular assembler receives $p_{device} \sim 14.2$ pW of continuous power when operated in single-band mode (e.g., from 1-2 atm or from 2-3 atm), or 56.8 pW when operated continuously in double-band mode (e.g., from 1-3 atm). Thus the device possesses a power density of $p_{device} / V_{ext} = 6.89\text{-}27.6 \times 10^9$ W/m^3. An acoustic power flux of $I_{acoustic} \sim p_{device} / S_{transducer} = 5070\text{-}20{,}300$ W/m^2 crossing an assembler of mean dimension $L_{assembler} \sim 100$ nm that is composed mostly of diamond having thermal conductivity $K_{diamond} = 2000$ W/m-K and heat capacity $C_V \sim 1.82 \times 10^6$ J/m^3-K produces a negligible equilibrium temperature differential of $\Delta T \sim I_{acoustic} L_{assembler} / K_{diamond} = 0.25\text{-}1.0 \times 10^{-6}$ K in an equilibration time of $t_{EQ} \sim L_{assembler}^2 C_V / K_{diamond} = 9 \times 10^{-12}$ sec.[228] Across a reaction chamber of size $L_{chamber} \sim 2$ microns, the spatial thermal gradient of $\Delta T_{chamber} / L_{chamber} \sim 3.9\text{-}15.7 \times 10^4$ K/m (taking $I_{fluid} = I_{acoustic}$ in Section B.3) caused by differential acoustic heating of liquid n-octane solvent on opposite sides of the reaction chamber implies that the solvent temperature at either end of the assembler may differ by as much as $\Delta T_{solvent,ends} = (\Delta T_{chamber} / L_{chamber}) X_{ext} \sim 0.01\text{-}0.05$ K, producing a linear thermal expansion in the diamond walls (expansion coefficient $\alpha_{diamond} = 8 \times 10^{-7}$ K^{-1}) that cannot be larger than $X_{ext} (\alpha_{diamond} \Delta T_{solvent,ends}) \sim 0.4\text{-}1.5 \times 10^{-14}$ m or $>10^{-4}$ atomic diameters, which is negligible.

B.4.4.2 Transient Cavitation

Ultrasound passing through liquids may produce transient bubbles which implode, producing temperature increases of $\sim 10^3$ K and pressure spikes of $\sim 10^3$ atm localized in regions of a few microns in radius. In water, normal or transient cavitation requires an irradiation intensity of $\sim 10^5$ W/m^2 (~ 5.4 atm) at 30 KHz or $\sim 10^6$ W/m^2 (~ 17 atm) at 1 MHz.[3258] Relevant thermodynamic constants for liquid n-octane lie within an order of magnitude of the same values for water, so 10 MHz operation in liquid n-octane at $I_{acoustic} \sim 6100$ W/m^2 for $\Delta P \sim 1$ atm (Section B.3) is not expected to produce transient cavitation. However, this expectation should be verified experimentally.

B.4.4.3 Stable Cavitation

Small pre-existing bubbles surrounded by a liquid will resonate in synchrony with the acoustic field, with the liquid acting as the oscillating mass and the gas serving as the compliant component. If the bubbles are pure acetylene gas, an oscillating compression that commonly reaches $P_{max} = 3$ atm might produce some decomposition which can occur in acetylene via slow deflagration above 2 atm at room temperature.[3141] Resonating bubbles have been reported in medical ultrasound beams at power intensities as low as 6800 W/m^2 at 0.75 MHz,[3258] which is slightly higher than $I_{acoustic} \sim 6100$ W/m^2. Pyrolysis of acetylene in argon bubbles in aqueous solution has also been observed at 20,000 W/m^2 and 1 MHz (Section B.4.1), but much higher intensities should be required to initiate bubble resonance at higher frequencies (e.g., at $\nu_{acoustic} = 10$ MHz). This expectation should be verified experimentally, and it would be prudent to ensure that no preexisting acetylene microbubbles are present in the n-octane feedstock solution.

Bubble size is also an important factor. Minnaert[3259] showed that under adiabatic conditions the resonant frequency $\nu_{resonant}$ of a bubble of gas of radius R_{bubble} with ratio of specific heats γ_{gas} in a liquid of density ρ_{liquid} and absolute liquid pressure P_{liquid} is given by $\nu_{resonant} = (3 \gamma_{gas} P_{liquid} / 4 \pi^2 \rho_{liquid})^{1/2} / R_{bubble} \sim 3.67 / R_{bubble}$ for acetylene gas bubbles in liquid n-octane at STP, taking $\gamma_{gas} \sim 1.23$, $P_{liquid} \sim 1$ atm (1.013×10^5 N/m^2), and $\rho_{liquid} \sim 702.5$ kg/m^3. The largest possible reaction chamber-sized bubble with $R_{bubble} = L_{chamber} / 2 = 1$ micron resonates at $\nu_{resonant} \sim 3.7$ MHz, a frequency only somewhat below $\nu_{acoustic}$. However, such colloidal bubbles may have lifetimes on the order of μsec.[3260] In particular, acetylene bubbles ~0.1 micron or smaller have a higher gas concentration inside the bubble than in solution, hence shrink rapidly (e.g., <8 μsec) via diffusion and redissolution. Since the assembler solvent bath is an ultrapure liquid with no nucleation sites, and since the acoustic wavelength in n-octane at 10 MHz is ~100 microns >> 2-micron reaction chamber width (suggesting isotropic pressure throughout the chamber), cavitation bubbles should be difficult to initiate.

Note that the natural acoustic resonance frequencies for the assembler structure itself are many orders of magnitude higher, on the order of $\nu_{resonance} > (\sim \nu_{sound} / L) = 50$ GHz taking $\nu_{sound} \sim 17{,}300$ m/sec for diamond structures of dimension $L \sim X_{ext} = 343.572$ nm. (Acoustic frequencies of 8 GHz were reported experimentally in liquid helium in the 1980s;[3261] frequencies up to 50 GHz can be used to see crystal defects in very good crystalline samples at liquid helium temperatures, and ultrasound in water is possible up to a few GHz.[3262])

B.4.4.4 Acoustic Heating

In conventional medical ultrasound,[228] dissipation of vibrational energy in aqueous tissues can produce heating rates of ~1 K/minute if applied at ~50,000 W/m^2 at 3 MHz, which is considered hazardous, and ultrasound intensities of $\sim 2 \times 10^7$ W/m^2 at the point of action are used to cauterize liver tissue after surgery.[3263] Continuous ultrasound exposure to 2000-6000 W/m^2 at 0.1-10 MHz raises human soft tissue temperature by 1 K at equilibrium, which is considered safe.[3264] Acoustic sonoluminescence in nonaqueous liquids[3151] typically requires power intensities in the range $0.4\text{-}3 \times 10^6$ W/m^2 >> $I_{acoustic} = 6100$ W/m^2. As noted at the top of this Section, both acoustically generated solvent thermal gradients and thermal expansion of the device are expected to be minor or insignificant factors.

B.4.4.5 Acoustic Torque and Fluid Streaming

Physical fluid motions are driven by ultrasonic radiation pressure,[3258] typically ~0.001 N/watt or ~0.23 pN near the largest ($X_{ext} Y_{ext}$) = 0.0344 micron^2 face of the assembler at $I_{acoustic} = 6100$ W/m^2. Forces of this magnitude are unlikely to significantly affect the structure or function of the proposed molecular assembler.

B.4.4.6 Shock Wave Formation

Shock waves most easily form in liquids having low attenuation but require macroscale path lengths much longer than the anticipated reaction chamber size $L_{chamber} \sim 2$ microns and may also require higher pulse pressures than the ~3 atm envisioned in the molecular assembler design (Section B.4.2). For example, a 3-MHz 10-atm pulse shows a shock waveform only after passing through 5 cm of water at room temperature.[3258]

B.4.5 Energy Efficiency and Energy Cost of Molecular Manufacturing

The overall energy efficiency of the proposed molecular assembler is very low. If each C-C bond in the final structure requires the dissipation of one C-C bond energy ($\sim$556 zJ)[208] and each C-H bond in the final structure requires the dissipation of one C-H bond energy ($\sim$671 zJ)[208] to install, this implies a theoretical minimum replication energy of $E_C \sim 1112$ zJ per carbon atom (half a bond energy, times four bonds per emplaced carbon atom) and $E_H \sim 671$ zJ per hydrogen atom installed or $E_{theoret} \sim E_C N_{C,device} + E_H N_{H,device} \sim 0.223$ nJ for the entire device. However, the 14.2-56.8 pW device actually receives a total of $E_{device} \sim p_{device} \tau_{repl} \sim$ 14,200-56,800 nJ of acoustic energy during each replication cycle (0.073-0.291 pJ per carbon atom), so replication energy efficiency is only $\varepsilon_{repl} = E_{theoret} / E_{device} \sim 0.001\%$. If energy is delivered efficiently to the onboard acoustic transducer, the energy cost of manufacturing could be as low as 3.8×10^{12} J/kg for an energy cost of $\sim$\$100,000/kg (cf. $\sim$\$6,880,000/kg for the active surfaces of computer chips and \$28,000,000/kg for gemstone quality diamond at wholesale; Table 6.1) assuming a raw energy cost of $\sim$\$0.10/KW-hr (2.78×10^{-8} \$/J). These high costs and poor efficiency may be significantly improved in successor designs.

B.5 Wall Stiffness During External Acoustic Forcing, Thermal Noise, or Collision

The proposed molecular assembler in its initial state may be viewed as an evacuated hollow rectangular box surrounded by fluid which is cyclically pressurized between 1-3 atm. This subjects each of the box walls to an oscillating pressure load which may cause each wall to bow out of plane. Each wall of the box is integrally joined to adjacent walls along each edge, hence each wall may be analyzed mechanically[3265] by analogy to a rectangular 1.5:1 clamped plate[3266] or to a >2:1 clamped strip plate.[3267] The maximum out-of-plane deflection at the center of a rectangular plate of shortest edge L_{plate}, thickness h_{plate}, and Young's modulus E_{plate}, when clamped on all four sides and loaded by uniform normal pressure ΔP_{plate}, is given by $\delta_{plate} = k_{plate} (\Delta P_{plate} L_{plate}^4 / E_{plate} h_{plate}^3)$, where k_{plate} is a constant of order $\sim$0.1.[3266,3267] The worst deflection occurs in the longest short wall where $L_{plate} = Y_{ext} = 110$ nm, $h_{plate} = w_{thick} = 10$ nm, and $E_{plate} = 1.05 \times 10^{12}$ N/m^2 for diamond. The highest applied pressure pulse is $\Delta P_{plate} = 3$ atm during a control pulse, giving $\delta_{plate} = 0.004$ nm, or $\Delta P_{plate} = 2$ atm during a power pulse, giving $\delta_{plate} = 0.003$ nm, both of which are <0.03 atomic diameter and thus should not affect placement accuracy during mechanosynthesis.

The in-plane stress pattern in a polycrystalline diamond film pressure sensor[3268] constructed of circular radius R_{film}, thickness h_{film}, Poisson's ratio k_{pois} and Young's modulus E_{film}, when clamped along the entire perimeter and loaded by normal pressure ΔP_{film}, is maximized at the center of the disk where radial and tangential strains are equal and the in-plane stretch displacement is given by $\delta_{stretch} = 3\, \Delta P_{film} R_{film}^3 (1 - k_{pois}^2) / 8\, E_{film} h_{film}^2$. Taking $\Delta P_{film} = 3$ atm, $R_{film} \sim 0.5\, X_{ext} = 110$ nm, $k_{pois} \sim 0.1$, $E_{film} = 1.05 \times 10^{12}$ N/m^2, and $h_{film} = 10$ nm, then in-plane wall stretch $\delta_{stretch} = 0.002$ nm or $<10^{-5}$ nm per carbon wall atom, which is orders of magnitude too small to affect atomic placement accuracy during mechanosynthesis.

The assembler shell must also be stiff enough to provide a base for positioning the Stewart platform to within a fraction of an atomic diameter near room temperature in the face of thermal noise. The bending stiffness of a clamped square plate of edge L_{plate}[3267] is given by $k_{bending} = E_{plate} h_{plate}^3 / (12\, L_{plate}^2 (1 - k_{pois}^2))$ and the positional uncertainty[208] of the plate surface due to thermal noise is $\delta_{bendingkT} \sim (kT / k_{bending})^{1/2}$. Taking $E_{plate} = 1.05 \times 10^{12}$ N/m^2, $h_{plate} = 10$ nm, $k_{pois} \sim 0.1$, $k = 1.381 \times 10^{-23}$ J/molecule-K, $T = 273.15$ K, and $L_{plate} \sim 110$ nm, then $k_{bending} = 7.3$ N/m and $\delta_{bendingkT} \sim 0.02$ nm or $\sim$0.1 atomic diameter, thus satisfying our minimal shell stiffness requirement. Stiffness scales as the cube of the wall thickness, so a small increase in wall thickness would be sufficient to compensate either for the uncertainties in this estimate or to increase stiffness and further reduce positional uncertainty if this proves necessary.

The present assembler shell design — essentially comprised of six solid walls forming a rectangular box — was selected for simplicity and was not optimized for stiffness achieved per wall atom. At the cost of increased structural complexity, wall atom count could be reduced without sacrificing stiffness by introducing hollow regions into the wall as, for example, in honeycomb plate,[3269] allowing thicker walls and drastically increasing stiffness. Introducing a single floor to ceiling beam in the middle of the floor would greatly increase stiffness for a very modest increase in atom count. Numerous other methods exist for improving stiffness with a similar number of atoms or for maintaining the same stiffness with fewer atoms. We do not explore these approaches here because the present design appears sufficient for our purposes.

Finally, during manufacturing operations the assembler, suspended in liquid n-octane, may collide with other objects of like size (e.g., parent or daughter assemblers, product objects, etc.) or with the walls of the reaction chamber. Both the sedimentation terminal velocity $v_{terminal} = 0.037$ micron/sec for an assembler falling in liquid n-octane at 1 g (Section B.1) and the Einstein diffusion velocity $v_{diffuse} \sim kT / 3\pi\, \eta_{solvent} L_{assembler}^2 \sim 58$ microns/sec for a diffusion distance of one mean assembler dimension $L_{assembler} \sim 100$ nm in solvent with absolute viscosity $\eta_{solvent} \sim 7.004 \times 10^{-4}$ Pa-sec (n-octane at 273.15 K)[3116] are dominated by the instantaneous assembler thermal velocity $v_{thermal} \sim (3\, kT / m_{assembler})^{1/2} = 64{,}000$ microns/sec.[228] A collisional impact of kinetic energy $E_{impact} = (1/2)\, m_{assembler} v_{thermal}^2 = 5.7$ zJ ($\sim$2 kT) wherein the colliding assembler is brought to a halt in one atomic diameter ($X_{halt} \sim 0.15$ nm) imparts an impact force of $F_{impact} = E_{impact} / X_{halt} = 38$ pN; given the high stiffness of diamond and a velocity of onset of the point force far below the speed of sound in diamond ($v_{thermal} << v_{diamond} = 17{,}300$ m/sec[208]), the applied pressure may be crudely approximated as a uniform normal pressure on a clamped plate, of order $\sim F_{impact} / X_{ext} Y_{ext} \sim 0.015$ atm $<< P_{max} = 3$ atm, yielding a negligible out-of-plane deflection of $\delta_{plate} \sim 0.00002$ nm and a negligible in-plane wall stretch of $\delta_{stretch} = 0.00001$ nm.

B.6 Wall Stiffness During Internal Mechanical Activities

During manufacturing operations, various mechanical forces are generated inside the assembler and are ultimately transmitted to the walls, possibly producing unwanted wall deflections. Typical forces may include up to $\sim$60 pN backpressure on the materials transport mechanisms, $\sim$568 pN during each double-band stroke of the acoustic transducer (Section B.4.2), and up to $\sim$17,740 pN for the most demanding possible mechanosynthetic operation which would involve the one-step mechanical decomposition of the acetylene triple carbon bond (a step not currently contemplated in any proposed mechanosynthetic sequence). Thus in the worst possible case, a mechanical point force of $F_{point} \sim 17{,}740$ pN applied to the center of the largest wall would produce the largest possible out-of-plane wall deflection. Given the high stiffness of diamond and a velocity of onset of the point force far below the speed of sound in diamond, the applied pressure may be crudely approximated as a uniform normal pressure on a clamped plate, of order $\sim F_{point} / X_{ext} Y_{ext} \sim 7$ atm ($\sim 2P_{max}$), yielding a very small out-of-plane deflection of $\delta_{plate} \sim 0.01$ nm and a negligible in-plane wall stretch of $\delta_{stretch} = 0.005$ nm. Applied point forces inside the molecular assembler will normally be 2 orders of magnitude smaller than this worst case condition.

Forced oscillations due to mechanical resonance with cyclically applied internal forces are highly unlikely because the assembler should have natural resonant frequencies of $\nu_{resonance}$ > 79 GHz (Section B.4.4.3) which are ~4 orders of magnitude above the driving frequency of $\nu_{acoustic}$ = 10 MHz, and also because the many mechanical structures attached to the inner surfaces of internal walls provide additional damping.

B.7 Wall Sublimation and Mechanical Depassivation Contamination

Wall materials potentially can sublimate into the interior vacuum of the device, the solid establishing equilibrium with its vapor at a temperature-dependent vapor pressure. However, this process should produce negligible effluent at room temperature for likely assembler building materials such as diamond.[228] A volumetric number density of less than one wall-material atom per V_{int} (0.00054 micron^3) — e.g., a perfect vacuum inside the assembler — equals a contaminant partial pressure of $<2 \times 10^{-11}$ atm. To reach this vapor pressure, pure carbon (e.g., graphite[3270]) must be heated to >2000 K; at an assembler operating temperature of ~273 K, the vapor pressure of fully bonded wall carbon can be estimated[3161,3271] as only ~10^{-133} atm. (The vapor pressures of various fullerenes at elevated temperatures have been measured[3272] as ~3×10^{-8} atm at 693 K[3273] and ~10^{-6} atm at 773 K[3274] for C_{60}.) Drexler[208] estimates the characteristic thermal cleavage time for unstressed 556 zJ C-C bonds in diamond as ~10^{85} sec at 300 K and ~10^{12} sec at 700 K.

In a perfect vacuum, unstressed polished hydrogenated diamond surfaces remain chemically and mechanically stable up to ~1275 K, although above this temperature the passivating hydrogens are removed and crystallographic surface reconstruction begins.[3275] Thus it is unlikely that passivating hydrogens on the interior surfaces of assembler diamond walls will spontaneously debond, contaminating the interior environment. The energy barrier for hydrogen abstraction from hydrogen passivated diamond surface has been estimated as ~7.7 kcal/mole[219] or ~53.5 zJ/atom, roughly the energy liberated by the application of a force of ~270 pN applied through a distance of ~ one atomic diameter. Since this is only slightly higher than forces commonly applied by the Stewart platform manipulators, a sufficiently sharp impact between such a manipulator and the inside walls could mechanically depassivate hydrogen into the device interior. Hydrogen atom bombardment of hydrogenated diamond surface has also been shown to abstract surface hydrogens.[3276,3277] However, this failure mode is unlikely to occur in a continuously positionally-controlled mechanosynthetic manufacturing environment.

Automatica, http://www.elsevier.com/locate/automatica or http://www.elsevier.com/locate/issn/00051098;
Autonomous Agents and Multi-Agent Systems, http://www.kluweronline.com/issn/1387-2532;
Autonomous Robots, http://www.kluweronline.com/issn/0929-5593;
BioSystems, http://www.elsevier.com/inca/publications/store/5/0/6/0/1/7/index.htt;
Bulletin of Mathematical Biology, http://www.academicpress.com/bmb;
Complexity, http://journals.wiley.com/complexity/;
Complexity International, http://www.csu.edu.au/ci/;
Complex Systems, http://www.complex-systems.com/;
Cybernetics and Systems, http://www.tandf.co.uk/journals/tf/01969722.html;
Desktop Engineering Magazine, http://www.deskeng.com;
Electronic Journal of Computational Kinematics, http://www-sop.inria.fr/coprin//EJCK/EJCK.html;
Engineering Computations: Intl. Journal for Computer-Aided Engineering and Software, http://pippo.emeraldinsight.com/vl=11750982/cl=29/nw=1/rpsv/ec.htm;
Evolution, http://lsvl.la.asu.edu/evolution/;
Evolutionary Computation, http://mitpress.mit.edu/journal-home.tcl?issn=10636560;
Genetic Programming and Evolvable Machines, http://www.wkap.nl/journalhome.htm/1389-2576 or http://www.kluweronline.com/issn/1389-2576;
Haptics-e: The Electronic Journal of Haptics Research, http://www.haptics-e.org/;
IEEE/ASME Transactions on Mechatronics, http://www.ieee-asme-mechatronics.org/;
IEEE/ASME Transactions on Micro-Electro-Mechanical Systems, http://www.trimmer.net/;
IEEE Control Systems Magazine, http://www.htc.honeywell.com/projects/CSM/;
IEEE Robotics & Automation Magazine, http://www.ncsu.edu/IEEE-RAS/RAM/RAM.html;
IEEE Transactions on Automatic Control, http://control.bu.edu/ieee/;
IEEE Transactions on Automation Science and Engineering, http://www.ieor.berkeley.edu/%7Egoldberg/t-ase/;
IEEE Transactions on Control Systems Technology, http://tcst.elen.utah.edu/;
IEEE Transactions on Evolutionary Computation, http://www.ewh.ieee.org/tc/nnc/pubs/tec/ or http://www.ieee.org/organizations/society/sp/tec.html;
IEEE Transactions on Nanotechnology, http://www.ieee.org/organizations/pubs/transactions/tnano.htm or http://www.ieee.org/transonnanotechnology;
IEEE Transactions on Robotics and Automation, http://www.ncsu.edu/IEEE-RAS/TRA/TRA.html;
Industrial Robot, http://lucia.emeraldinsight.com/vl=4420118/cl=36/nw=1/rpsv/ir.htm or http://pippo.emeraldinsight.com/vl=11750982/cl=29/nw=1/rpsv/ir.htm;
Informatica, http://www.mii.lt/mii_inform/;
Information Processing Society of Japan (IPSJ) Transactions, http://www.ipsj.or.jp/english/trans_e.html or http://www.ipsj.or.jp;
Integrated Computer-Aided Manufacturing, http://www.iospress.nl/site/html/10692509.html;
Integrated Manufacturing Systems, http://giorgio.emeraldinsight.com/vl=2375813/cl=37/nw=1/rpsv/ims.htm;
InterJournal, http://www.interjournal.org;
International Journal of Mechatronics, http://www.elsevier.nl/locate/inca/933;
International Journal of Robotics Research, http://www.ijrr.org/ and http://www.sagepub.com/journal.aspx?pid=247;
Journal of Artificial Societies and Social Simulation (JASSS), http://jasss.soc.surrey.ac.uk/JASSS.html;
Journal of Automation and Information Sciences, http://www.begellhouse.com/journals/2b6239406278e43e.html;
Journal of Computational and Theoretical Nanoscience, http://www.aspbs.com/ctn/index.htm;
Journal of Evolution and Technology, http://www.jetpress.org/index.html;
Journal of Intelligent and Robotic Systems, http://www.kluweronline.com/issn/0921-0296 and http://www.wkap.nl/journalhome.htm/0921-0296;
Journal of Mechanical Design, http://ojps.aip.org/ASMEJournals/MechanicalDesign/;
Journal of Microelectromechanical Systems; Journal of Robotics and Mechatronics, http://www.hfl.hiroshima-u.ac.jp/jrm/;
Journal of Micromechatronics, http://www.vsppub.com/journals/jn-JouMic.html;
Journal of Nanoscience and Nanotechnology, http://www.aspbs.com/jnn/index.htm;.
Journal of Nonlinear Phenomena in Complex Systems, Belarus, http://www.j-npcs.org/;
Journal of Robotic Systems, http://www.interscience.wiley.com/jpages/0741-2223/;
Journal of Theoretical Biology, http://www.academicpress.com/jtb;
Journal of the Robotics Society of Japan, http://www.cs.arizona.edu/japan/www/rsj/rsj.html;
Mechanism and Machine Theory, http://www.elsevier.com/inca/publications/store/3/0/3/;
Mechatronics, http://www.elsevier.com/locate/mechatronics or http://www.elsevier.nl/inca/publications/store/9/3/3/;
Microsystem Technologies, http://link.springer.de/link/service/journals/00542/about.htm;
Nonlinear Phenomena in Complex Systems, http://www.ac.by/publications/npcs/;
Physica D (Nonlinear Phenomena), http://www.elsevier.nl/inca/publications/store/5/0/5/7/1/4/505714.pub.htt;
Presence: Teleoperators and Virtual Environments, http://www-mitpress.mit.edu/catalog/item/default.asp?ttype=4&tid=37;
Progress in Complexity, Information and Design, http://www.iscid.org/pcid.php;
Robotica, http://titles.cambridge.org/journals/journal_catalogue.asp?historylinks=ALPHA&mnemonic=ROB;
Rapid Prototyping Journal, http://ceres.emeraldinsight.com/vl=7188318/cl=49/nw=1/rpsv/rpj.htm and http://www.ingenta.com/journals/browse/mcb/156.
Robotics and Autonomous Systems, http://www.elsevier.nl/locate/robot and http://www.elsevier.com/inca/publications/store/5/0/5/6/2/2/;
Robotics and Computer-Integrated Manufacturing, http://www.elsevier.nl/locate/rcim.

22. "Design Automation Laboratory," Arizona State University; http://asudesign.eas.asu.edu/.
23. "Industrial and Manufacturing Engineering," California Polytechnic State University; http://www.ime.calpoly.edu/.
24. "Bachelor of Science in Mechatronic Engineering," California State University at Chico; http://www.ecst.csuchico.edu/__depts/mem/BS_Mechatronic_Engineering/index.html or http://www.ecst.csuchico.edu/__depts/mem/.
25. "Advanced Mechatronics Laboratory (AML)," Carnegie Mellon University, http://www-2.cs.cmu.edu/afs/cs.cmu.edu/project/chimera/www/aml.html; Carnegie Mellon Robotics Institute, http://www.ri.cmu.edu/; mechatronics class syllabus, http://www.ece.cmu.edu/~fedder/mechatronics/Syllabus.html.
26. "Clemson University Mechatronics," Clemson University, http://ece.clemson.edu/crb/; "Research Projects," Robotics and Mechatronics Laboratory, http://ece.clemson.edu/crb/research/projects.htm. See also: Christopher D. Rahn, Darren M. Dawson, Frank W. Paul, "Development of a Cross-Disciplinary Mechatronics Course"; http://fie.engrng.pitt.edu/fie95/4a1/4a13/4a13.htm.
27. Dr. David G. Alciatore, PE, Colorado State University; http://www.engr.colostate.edu/~dga/. See also http://www.engr.colostate.edu/~dga/dga/courses.html.
28. "Institute of Robotics and Mechatronics," Deutsches Zentrum fur Luft- und Raumfahrt (DLR), Germany; http://www.op.dlr.de/FF-DR/ff_dr_homepage_engl.html.
29. "Georgia Tech Mobile Robot Lab," Georgia Institute of Technology; http://www.cc.gatech.edu/ai/robot-lab/.
30. Gregory S. Chirikjian, Yu Zhou, Sangyoon Lee, Jackrit Suthakorn, "Mechatronics: ME 530.421 Spring 2003," Department of Mechanical Engineering, Johns Hopkins University, 2003; http://custer.me.jhu.edu/mechatronics/syllabus2003.htm.
31. "Mechatronics Research Group," Loughborough University, U.K.; http://info.lboro.ac.uk/research/mechatronics/.
32. "Precision Systems Design and Manufacturing," Massachusetts Institute of Technology (MIT), http://psdam.mit.edu/; "Laboratory for Manufacturing and Productivity (LMP), http://web.mit.edu/lmp/www.
33. "Mechatronikai," Mechatronical Secondary Vocational School, Budapest, Hungary; http://www.mechatronika.hu.

34. "ME 491/602: Mechatronic System Modeling and Simulation," Department of Mechanical Engineering, Michigan State University; http://www.egr.msu.edu/classes/me491-602/clo.html.
35. "The Advanced Manufacturing and Mechatronics Centre (AMMC)," Middlesex University, U.K.; http://www.mdx.ac.uk/www/ammc/ammc.html.
36. "Mechatronics," North Carolina State University; http://mechatronics.mae.ncsu.edu/.
37. "Mechatronics at Rensselaer," Rensselaer Polytechnic Institute; http://www.rpi.edu/~craigk/.
38. "ELEC 201(F): An Introduction to Engineering Design," Rice University; http://www-ece.rice.edu/Courses/201/course.html.
39. "SDSU Mechatronics," San Diego State University; http://kahuna.sdsu.edu/~mechtron/mechatronics/.
40. "Mechatronics at San José State University," College of Engineering, San Jose State University, http://www.engr.sjsu.edu/bjfurman/mechatronics/; "ME 106 — Fundamentals of Mechatronics," http://www.engr.sjsu.edu/bjfurman/courses/ME106/.
41. "Mechatronics and Control Research Group," South Bank University, London; http://www.sbu.ac.uk/~sesd/research/mechatronics.html.
42. "Home to the Mechatronics Courses at Stanford University," Smart Product Design Laboratory, Stanford University; http://design.stanford.edu/spdl/; "Center for Design Research," http://www-cdr.stanford.edu/CDR/cdr.html.
43. "Dragon," second stage of PIRAIA Project, Swedish Institute of Computer Science; http://www.sics.se/~mn/dragon2.htm.
44. Institute of Robotics, Swiss Federal Institute of Technology Zurich (ETHZ), Switzerland; http://www.ifr.mavt.ethz.ch/.
45. "Mechatronics," University of California at Berkeley, http://me.berkeley.edu/mechatronics.html; "Mechatronics Design Lab / EE192," http://www-inst.eecs.berkeley.edu/~ee192/.
46. "Mechanical Engineering and Mechatronics," University of Dundee, U.K.; http://www.dundee.ac.uk/mecheng/.
47. Design and Rapid Prototyping Laboratory, Department of Mechanical and Aerospace Engineering, University of Florida; http://www.mae.ufl.edu/~akumar/research/testbed.htm.
48. "UIUC College of Engineering Mechatronics Laboratory," University of Illinois at Urbana-Champaign, http://robot0.ge.uiuc.edu/~spong/deere/.
49. "Mechatronik Homepage," Johannes Kepler University of Linz, Austria; http://www.mechatronik.uni-linz.ac.at/.
50. "Mechatronics Research Group," Department of Mechanical and Manufacturing Engineering, University of Melbourne, Australia; http://www.mame.mu.oz.au/mechatronics/.
51. Mechatronic Engineering program, University of Southern Denmark, Sonderborg, Denmark; http://www.sdu.dk/E/Soenderborg.html.
52. "Drebbel Institute for Mechatronics," University of Twente, The Netherlands; http://www.drebbel.utwente.nl/.
53. Satya Krosuri, "Mechatronics Main Page" and "ME3200/ME3210 Mechatronics," University of Utah; http://www.mech.utah.edu/~me3200/.
54. "Mechatronics Engineering Degree Programmes," University of Western Australia; http://www.mech.uwa.edu.au/jpt/mecha/course.html.
55. "Center for Intelligent Mechatronics," Vanderbilt University; http://fourier.vuse.vanderbilt.edu/cim/index.html.
56. "Virginia Tech Mechatronics," Virginia Polytechnic Institute; http://mechatronics.me.vt.edu/. See also http://www.ecpe.vt.edu/ecenews/feb97/mchtrn.html.
57. Center for Automation Technologies, Rensselaer Polytechnic Institute, 2002; http://www.cat.rpi.edu/r&d.htm.
58. Center for International Research on MicroMechatronics (CIRMM), Institute of Industrial Science, University of Tokyo; http://www.iis.u-tokyo.ac.jp/english/cgi/daibumon.cgi?daibumon_id=8.
59. "Research Opportunities in Biomolecular Nanotechnology at ASU," Arizona State University; http://photoscience.la.asu.edu/bionano/research.htm.
60. "Nano & Micromechanics Laboratory," Brown University; http://en732c.engin.brown.edu/.
61. "NASA Sponsored Computational Nanotechnology Project, Atomistic Design and Simulations of Nanoscale Machines and Assembly," California Institute of Technology, http://www.wag.caltech.edu/gallery/gallery_nanotec.html; "Materials and Process Simulation Center," California Institute of Technology, http://www.wag.caltech.edu/; "Roukes Group," California Institute of Technology, http://nano.caltech.edu/home.html.
62. "NanoRobotics Laboratory," Carnegie Mellon University; http://www.me.cmu.edu/faculty1/sitti/nano/ or http://www.cs.cmu.edu/~msitti/.
63. "The Physics of NEMS and MEMS," Craighead Research Group, Cornell University; http://www.hgc.cornell.edu/nems/index.htm.
64. "NanoRobotics Laboratory," Ecole Polytechnique Montreal, Canada; http://www.nano.polymtl.ca/en/index.html.
65. IEEE Nanotechnology Council, TC-1: Technical Committee on Nanorobotics and Nanomanufacturing; http://www.cs.cmu.edu/~msitti/tc1.html.
66. "Micro-Nano Mechatronics," Fukuda Laboratory, Nagoya University, Japan, http://www.mein.nagoya-u.ac.jp/activity/2001_e/micro.html.
67. "Institute for Nanotechnology," Northwestern University; http://www.nanotechnology.northwestern.edu/.
68. "Nanofabrication Manufacturing Technology (2 NMT)… Associate in Engineering Technology degree in Nanofabrication Manufacturing Technology," Pennsylvania State University; http://www.psu.edu/bulletins/bluebook/major/2_nmt.htm.
69. "Micro & Nano Manufacturing, Microsystem Design, Assembly and Packaging," Center for Automation Technologies, Rensselaer Polytechnic Institute; http://www.cat.rpi.edu/.
70. "Nanomanufacturing Facility," CBEN, Rice University; http://www.ruf.rice.edu/~cben/Nanomanufacturing.shtml.
71. Constantinos Mavroidis, Martin L. Yarmush, Atul Dubey, Angela Thornton, Kevin Nikitczuk, Silvina Tomassone, Fotios Papadimitrakopoulos, Bernie Yurke, "Protein based nano-machines for space applications," Report to the NASA Institute for Advanced Concepts, December 2002; http://bionano.rutgers.edu/Mavroidis_Final_Report.pdf; research website "Bio-Nano Robotics" at http://bionano.rutgers.edu/. See also: "Dinos Mavroidis Interview", 15 December 2002; http://nanotech-now.com/Mavroidis-interview-12152002.htm.
72. "Manufacturing Systems and Robotics," Ecole Polytechnique Federale de Lausanne; http://www2.epfl.ch/Jahia/site/graduateschool/pid/7219.
73. "Nanotechnology Group," Swiss Federal Institute of Technology Zurich (ETHZ); http://www.nanotechnology.ethz.ch/.
74. "Mechatronics," Technische Universitat Ilmenau; http://www.tu-ilmenau.de/englisch/bildung/mechatronik/mechatronik.html.
75. "Nanomechatronics: Master Level Course Plan," School of Engineering, Tohoku University; http://www.eng.tohoku.ac.jp/syllabus/2003/subject/2138-e.html and http://www.eng.tohoku.ac.jp/syllabus/2003/dept/kiden-m-e.html.
76. "Zettl Research Group," University of California at Berkeley; http://physics.berkeley.edu/research/zettl/projects/TEMManip.html.
77. "Montemagno Research Group," http://www.biomotors.ucla.edu/; Xiang Zhang, "Micro- nano scale engineering,… micro and nano-devices, nano-lithography and nano-instrumentation," University of California at Los Angeles, http://www.mae.ucla.edu/academics/faculty/zhang.htm.
78. "Yu Research on Nanoscale Mechanics and Physics," University of Illinois at Urbana-Champaign; http://www.staff.uiuc.edu/~mfyu/group/.
79. "Description of Research Activities, DNA- and Bio-Nanotechnology," University of Minnesota; http://www.nano.umn.edu/omni/research/sub2.html.
80. "Nanoscale Science Research Group," University of North Carolina at Chapel Hill; http://www.cs.unc.edu/Research/nano/.
81. "Laboratory for Molecular Robotics," University of Southern California, http://www-lmr.usc.edu/~lmr/; "CS 549 Nanorobotics Spring 2003," http://www-pal.usc.edu/cs5xx/index.html; "Molecular Robotics: Nanoscale Manipulation," http://www-rcf.usc.edu/~koel/Topic10.html.
82. "Laser, MEMS, Nanoengineering," University of Texas at Austin, http://www.me.utexas.edu/~scchen/; "NIH Biotechnology Training Grant — Molecular Sensors and Nanobiotechnology," University of Texas at Austin, http://www.bme.utexas.edu/nihtg/curriculum.html.
83. Hideki Kawakatsu, "Kawakatsu Laboratory," Institute of Industrial Science, University of Tokyo, Japan, http://pico.iis.u-tokyo.ac.jp/; "Tele-Nanorobotics," University of Tokyo, Japan, http://chan.iis.u-tokyo.ac.jp/~shintani/Nano/.
84. Sergey Edward Lyshevski, "Chapter 6. Mechatronics: New Directions in Nano-, Micro-, and Mini-Scale Electromechanical Systems Design, and Engineering Curriculum Development," CRC Press, 2002; http://mechatronics.ece.usu.edu/2003/mechatronics_handbook/0066ch06.pdf.
85. Dynamical and Evolutionary Machine Organization Laboratory, Computer Science Department, Center for Complex Systems, Brandeis University; http://www.demo.cs.brandeis.edu/index.html.
86. Brunel University, U.K.; http://www.brunel.ac.uk/depts/AI/alife/.

87. Avida Artificial Life Group, California Institute of Technology; http://www.krl.caltech.edu/avida/Avida.html.
88. Computational Synthesis Laboratory, Cornell University; http://www.mae.cornell.edu/ccsl/. See also Hod Lipson, "Research Fields…Self Replication," http://www.mae.cornell.edu/lipson/.
89. DCU Artificial Life Laboratory, School of Electronic Engineering, Dublin City University, Ireland; http://www.eeng.dcu.ie/~alife/.
90. Équipe Évolution Artificielle et Apprentissage, École Polytechnique, France; http://blanche.polytechnique.fr/www.eeaax/eeaax.html.
91. Genetic Algorithms Group, George Mason University; http://www.cs.gmu.edu/research/gag/.
92. Adaptive Systems Group, German National Research Centre for Information Technology, Germany; http://borneo.gmd.de/AS/pages/as.html.
93. Department of Adaptive Systems, Institute of Isotopes of the Hungarian Academy of Sciences and the University of Szeged; http://iserv.iki.kfki.hu/adaptlab.html.
94. Artificial Life Group, Iowa State University; http://www.cs.iastate.edu/~honavar/alife.isu.html.
95. Liverpool Bicomputation Group, Liverpool University, U.K.; http://www.csc.liv.ac.uk/~biocomp/.
96. Artificial Life Group, Massachusetts Institute of Technology, Cambridge, Massachusetts; http://www.ai.mit.edu/people/cmaley/alife/.
97. Genetic Algorithms Research and Applications Group, Michigan State University; http://isl.msu.edu/GA/ or http://GARAGe.cps.msu.edu.
98. Arita group, Artificial Life Laboratory, Nagoya University, Japan; http://www2.create.human.nagoya-u.ac.jp/~ari/.
99. Evolutionary Computation Research Group, Napier University, U.K.; http://www.dcs.napier.ac.uk/evol/home.html.
100. Research Group on Artificial Life (GRAL), National Research Council (CNR), Rome, Italy; http://gral.ip.rm.cnr.it/.
101. New England Complex Systems Institute (NECSI), Cambridge, MA; http://necsi.org/.
102. Artificial Life Project, Reed College; http://alife.reed.edu/.
103. Santa Fe Institute; http://www.santafe.edu/.
104. Unemi Laboratory, Department of Information Systems Science, Soka University, Japan; http://www.intlab.soka.ac.jp/~unemi/Labo.html.
105. Logic Systems Laboratory, Swiss Federal Institute of Technology, Switzerland; http://lslwww.epfl.ch/.
106. Evolutionary and Neural Systems Exploration (SENSE) Research Group, Syracuse University; http://www.cis.syr.edu/~mohan/html/research.html.
107. L-Systems Group, Trinity College, Hartford; http://shakti.trincoll.edu/~cschneid/lsystems.html.
108. Geneura Team, Departamento de Arquitectura y Tecnología de los Computadores, Universidad de Granada, Spain; http://geneura.ugr.es/OLD/en/.
109. Artificial Life and Complex Systems group, Department of Computer Science, Universitat Dortmund, Germany; http://ls11-www.cs.uni-dortmund.de/alife/.
110. Artis Project, Computational Science Section, Universiteit van Amsterdam, The Netherlands; http://artis.phenome.org.
111. Genetic Programming Group, University College London, U.K.; http://www.cs.ucl.ac.uk/intelligent_systems/genetic_programming.html.
112. EVALife: Evolutionary Computation and Artificial Life, University of Aarhus, Denmark; http://www.evalife.dk/.
113. Artificial Life Group at Aizu, University of Aizu, Japan; http://www.u-aizu.ac.jp/~nehaniv/ALGA.html.
114. Evolutionary Computation Group, University of Edinburgh, U.K.; http://www.dai.ed.ac.uk/groups/evalg/.
115. Sayama Lab, Complex Systems Laboratory, University of Electro-Communications, Tokyo, Japan; http://complex.hc.uec.ac.jp/.
116. Natural Selection Group, University of Guelph, Canada; http://hebb.cis.uoguelph.ca/home/ns.html.
117. Adaptive Systems Research Group, University of Hertfordshire, U.K.; http://homepages.feis.herts.ac.uk/~nehaniv/ASRG.html.
118. Digital Genetic Research Group, University of Idaho; http://www.cs.uidaho.edu/~foster/research/.
119. Illinois Genetic Algorithms Laboratory, University of Illinois at Urbana-Champaign; http://gal4.ge.uiuc.edu/ or http://www-illigal.ge.uiuc.edu/index.php3.
120. Symbolic Optimization Research Group, University of Newcastle upon Tyne, U.K.; http://lorien.ncl.ac.uk/sorg/.
121. Adaptive Computational Group, Computer Science Department, University of New Mexico; http://www.cs.unm.edu/~forrest/adaptive-web/ac_main.htm.
122. Investigations in Computational Rationality, University of Pennsylvania; http://opim.wharton.upenn.edu/users/sok/comprats/ourdocs.html.
123. Evolutionary Optimization Group, University of Southampton, U.K.; http://www.soton.ac.uk/~ajk/opt/welcome.html.
124. Evolutionary and Adaptive Systems, Department of Informatics, University of Sussex, U.K.; http://www.cogs.susx.ac.uk/easy/ and http://www.sussex.ac.uk/informatics/. See also: Centre for Computational Neuroscience and Robotics (CCNR); http://www.cogs.susx.ac.uk/ccnr/.
125. Evolutionary Computing Group, University of the West of England at Bristol, U.K.; http://www.btc.uwe.ac.uk/evol/index.html.
126. Ikegami Laboratory, Complex Systems and Artificial Life, University of Tokyo, Japan; http://sacral.c.u-tokyo.ac.jp/.
127. Hiroki Sayama, "Intensive Course on Complex Systems Science II: Invitation to Self-Replication Studies," part-time lecture held at the Department of Complex Systems Science, Graduate School of Information Science, Nagoya University, Japan, Summer 2003; http://complex.hc.uec.ac.jp/h15-nagoya (restricted access only).
128. Pavel O. Luksha, personal communication to Robert A. Freitas Jr., 9 October 2003.
129. Jack Uldrich, "'Exponential' Thinking for the Future," Tech Central Station, 21 January 2004; http://remotefarm.techcentralstation.com/012104D.html.
130. Arthur C. Clarke, Address to the 4th International Symposium on Bioastronautics and the Exploration of Space, 1968; in Arthur C. Clarke, Report on Planet Three and Other Speculations, Harper Collins, New York, 1972.
150. Michael Denton, "Chapter 3. Organism and Machine: The Flawed Analogy," in Jay W. Richards, ed., Are We Spiritual Machines? Ray Kurzweil vs. the Critics of Strong A.I., Discovery Institute, Seattle, WA, 2002, pp. 78-97; http://www.kurzweilai.net/meme/frame.html?main=/meme/memelist.html?m%3D19; see also http://www.kurzweilai.net/meme/frame.html?m=19 with Kurzweil's response in Chapter 7.
151. John Mymer, The Paleolithic Age, Palgrave Macmillan, 1982.
152. Donald E. Tyler, Earliest Man of America in Oregon, U.S.A., with photographs of Paleolithic artifacts, Discovery Books, 1986.
153. Ronald Singer, Bruce G. Gladfelter, John J. Wymer, The Lower Paleolithic Site at Hoxne, England, University of Chicago Press, 1993.
154. Fred Wendorf, Romuald Schild, Angela E. Close, Egypt During the Last Interglacial: The Middle Paleolithic of Bir Tarfawi and Bir Sahara East, Plenum Publishing Corp., 1993.
155. Olga Soffer, The Upper Paleolithic of the Central Russian Plain, Academic Press, New York, 1997.
156. Donald E. Tyler, American Paleolithic: Boat Building Eight Million Years Ago, Discovery Books, 1999.
157. J.E. Scott-Jackson, ed., Lower and Middle Paleolithic Artifacts from Deposits Mapped as Clay-with-Flints, Ox Bow Press, 2000.
158. Margherita Mussi, Earliest Italy: An Overview of the Italian Paleolithic and Mesolithic, Kluwer Academic Publishers, 2001.
159. R.F. Tylecote, History of Metallurgy, Second Edition, Ashgate Publishing Company, 1992; Michael S. Bisson, S. Terry Childs, Philip De Barros, Augusti Holl, Ancient African Metallurgy: The Sociocultural Context, Altamira Press, 2000.
160. I.J. Thorpe, The Origins of Agriculture in Europe, Routledge, 1999; K.D. White, Agricultural Implements and Farm Equipment in the Roman World, Johns Hopkins University Press, Baltimore, MD, 2002.
161. John William Humphrey, John Peter Oleson, Andrew N. Sherwood, eds., Greek and Roman Technology, A Sourcebook: Annotated Translations of Greek and Roman Texts and Documents, Routledge, 1998.
162. Stephen Selby, "A Crossbow Mechanism with Some Unique Features from Shandong, China," 2001; http://www.atarn.org/chinese/bjng_xbow/bjng_xbow.htm.
163. Hong-Sen Yan, The Beauty of Ancient Chinese Locks, Ancient Chinese Machines Research Foundation, Tainan, Taiwan, June 1999 (ISBN 957-97374-9-5). In Chinese.
164. Willis I. Milham, Time and Timekeepers, The Macmillan Company, New York, 1944.
165. John G. Landels, Engineering in the Ancient World, University of California Press, 1981.

166. E.J. Dijksterhuis, Archimedes, Princeton University Press, Princeton, NJ, 1987.
167. Sir Ralph Payne-Gallwey, The Crossbow, Mediaeval and Modern, Military and Sporting, its Construction, History & Management with a Treatise on Balista and Catapult of the Ancients, and an Appendix on the Catapult, Balista & the Turkish Bow, The Holland Press, London, 1995; Michael Woods, Mary B. Woods, Ancient Warfare: From Clubs to Catapults, Runestone Press, 2000.
168. Sarah Underhill Wisseman, Wendell S. Williams, eds., Ancient Technologies and Archeological Materials, Routledge, 1994.
169. "Section 40. On an Apple being lifted, Hercules shoots a Dragon which then hisses," from: Bennet Woodcroft (translator and editor), The Pneumatics of Hero of Alexandria, from the Original Greek, Taylor Walton and Maberly, London, 1851; http://www.history.rochester.edu/steam/hero/section40.html.
170. Derek de Solla Price, Gears from the Greeks, Science History Publications, New York, 1975; Derek de Solla Price, "Gears from the Greeks: The Antikythera mechanism — a calendar computer from ca. 80 BC," Trans. Amer. Philos. Soc. 64(1974):1-70; Derek J. de Solla Price, "An ancient Greek computer," Sci. Amer. 200(June 1959):60-67; http://www.giant.net.au/users/rupert/kythera/kythera3.htm. Antikythera mechanism links: http://www.giant.net.au/users/rupert/kythera/kythera5.htm; http://etl.uom.gr/mr/Antikythera/;
171. Gerald M. Levitt The Turk, Chess Automaton, McFarland & Company, 2000.
172. Tom Standage, The Turk: The Life and Times of the Famous Eighteenth-Century Chess-Playing Machine, Walker & Co., 2002.
173. Alfred Chapuis, Edmond Droz (Alec Reid, transl.), Automata: A Historical and Technological Study, B.T. Batsford Ltd., London, 1958; D. J. de Solla Price, "Automata and the origins of mechanism and mechanistic philosophy," Technology and Culture 5(Spring 1964):9-23; Silvio Bedini, "The role of automata in the history of technology," Technology and Culture 5(Spring 1964):24-42; Christen Bailly, Automata, the Golden Age: 1848-1914, Harper and Row, New York, 1987. See also: http://www.nyu.edu/pages/linguistics/courses/v610051/gelmanr/ling.html; http://access.tucson.org/~michael/cb_intro.html.
174. Bruce Mazlish, The Fourth Discontinuity: The Co-Evolution of Humans and Machines, Yale University Press, 1993.
175. Gaby Wood, Edison's Eve: A Magical History of the Quest for Mechanical Life, Knopf, New York, 2002; http://books.guardian.co.uk/extracts/story/0,6761,650977,00.html.
176. Etienne Benson, "Science historian examines the 18th-century quest for artificial life," Stanford Report, 19 October 2001; http://news-service.stanford.edu/news/october24/riskinprofile-1024.html. See also: http://shoko.calarts.edu/~sroberts/articles/DeVaucanson.duck.html; http://music.calarts.edu/~sroberts/articles/DeVaucanson.duck.html; http://www.nyu.edu/pages/linguistics/courses/v610051/gelmanr/cult_hist/text/p240.html.
177. Sigvar Strandh, The History of the Machine, Dorset Press, New York, 1979; e.g., http://music.calarts.edu/~sroberts/articles/DeVaucanson.duck.html.
178. E.B. Carne et al, "A self-organizing binary logic element," in Eugene E. Bernard, Morley R. Kare, eds., Biological Prototypes and Synthetic Systems, Vol. I, Plenum Press, New York, 1962, pp. 311-330.
179. Nicholas V. Findler, Wiley R. McKinzie, "Computer simulation of a self-preserving and learning organism," Bull. Math. Biophys. 31(1969):247-253.
180. W. Grey Walter, "An imitation of life," Sci. Am. 182(May 1950):42-45; W. Grey Walter, "A machine that learns," Sci. Am. 185(August 1951):60-63; W. Grey Walter, The Living Brain, N.W. Norton & Co., New York, 1953; W. Grey Walter, "Imitation of life," Scientific American Reader, Simon and Schuster, New York, 1953, pp. 545-551; Owen E. Holland, "Grey Walter: The pioneer of real Artificial Life," in Christopher Langton, ed., Proc. 5th Intl. Workshop on Artificial Life, MIT Press, Cambridge, MA, 1997, pp. 34-44. See also: "Machina Speculatrix", http://www.plazaearth.com/usr/gasperi/walter.htm.
181. M.F. Huber; "Free roving machine," Wireless World 78(December 1972):593-594.
182. Edmund C. Berkeley, "The construction of living robots — Part I," Computers and Automation 21(August 1972):27-32.
183. Valentino Braitenberg, Vehicles: Experiments in Synthetic Psychology, MIT Press, Cambridge, MA, 1984.
184. Joseph L. Jones, Anita M. Flynn, Mobile Robots: Inspiration to Implementation, A.K. Peters Ltd., Wellesley, MA, 1993.
185. B. Hasslacher, M.W. Tilden, "Living machines," Robotics and Autonomous Systems 15(July 1995):143-169; online draft dated 14 June 1994, http://www.solarbotics.net/library/pdflib/pdf/living_machines.pdf. Reprinted as: B. Hasslacher, M.W. Tilden, "Living Machines," in L. Steels, ed., Robotics and Autonomous Systems: The Biology and Technology of Intelligent Autonomous Agents, Springer-Verlag, New York, 1995, pp. 1-36.
186. Rodney Brooks, Cambrian Intelligence: The Early History of the New AI, MIT Press, Cambridge, MA, 1999.
187. Rene Descartes, Traite de l'homme (Treatise on Man), composed ca. 1633, published posthumously in 1664; reprinted in John Cottingham, Robert Stoothoff, Dugald Murdoch, transl., The Philosophical Writings of Rene Descartes, Vol. 1, Cambridge University Press, Cambridge, U.K., 1985, pp. 99-107. See also: "Animals are machines," reprinted in Tom Regan, Peter Singer, eds., Animal Rights and Human Obligations, Prentice-Hall, Inc., NJ, 1976, pp. 60-66.
188. Samuel Butler, Erewhon, J.M. Dent and Sons, Ltd., Aldine House, Bedford Street, London, 1932; First Edition, 1872. See at: http://www.hoboes.com/html/FireBlade/Butler/Erewhon/.
189. Francis Fukayama, Jacques Attali, "The beginning of a new history," New Perspectives Quarterly 17(Summer 2000); http://www.digitalnpq.org/archive/2000_summer/new_beginning.html or Pugwash Online: http://www.pugwash.org/reports/pim/pim17.htm.
190. Moshe Sipper, James A. Reggia, "Build your own replicator," Sci. Amer. 285(August 2001):38-39.
191. Therese Lowery, "BEAM Robotics," 26 August 1999; http://www.nis.lanl.gov/projects/robot//philosophy.html. See also: Brian O. Bush, "The BEAM FAQ," 10 December 1998; http://people.ne.mediaone.net/bushbo/beam/FAQ.html. See also: Dave Hrynkiw, Mark W. Tilden, Junkbots, Bugbots, and Bots on Wheels: Building Simple Robots with BEAM Technology, McGraw-Hill Osborne Media, New York, 2002.
192. Robert Jastrow, The Enchanted Loom: Mind in the Universe, Simon and Schuster, New York, 1981.
193. Scott Adams, Shave the Whales, Andrews McMeel Publishing, Kansas City, MO, 1994, p. 88.
194. William Paley, Natural Theology: or Evidences of the Existence and Attributes of the Deity, Collected from the Appearances of Nature, Chapter i, Section 1, E. Goodale, 1802; http://www.hti.umich.edu/cgi/p/pd-modeng/pd-modeng-idx?type=HTML&rgn=TEI.2&byte=53049319 (12th Edition, 1809). See also: Michael Ruse, ed., Philosophy of Biology, 1998, pp. 36-40; Richard Lenski, "Twice as natural," Nature 414(15 November 2001):255.
195. Alexander J. Cohen, "Erewhon: Self-Reproducing Machines"; http://cinemaspace.berkeley.edu/AlexCohen/Erewhon-Self-Rep.pdf.
196. John Desmond Bernal, The World, the Flesh, and the Devil: An Enquiry into the Future of the Three Enemies of the Rational Soul, reprint of the 1929 essay, Indiana University Press, Bloomington, 1969. See also at: http://www.hia.com/pcr/bernal.html.
197. K. Eric Drexler, "Molecular engineering: an approach to the development of general capabilities for molecular manipulation," Proc. Natl. Acad. Sci. (USA) 78(September 1981):5275-5278.
198. K. Eric Drexler, "Molecular nanomachines: Physical principles and implementation strategies," Annu. Rev. Biophys. Biomol. Struct. 23(1994):377-405.
199. K. Eric Drexler, Engines of Creation: The Coming Era of Nanotechnology, Anchor Press/Doubleday, New York, 1986; http://www.foresight.org/EOC/.
200. Moshe Sipper, "Fifty Years of Research on Self-Replication: An Overview," Artificial Life 4(Summer 1998):237-257, in "Special Issue on Self-Replication." See also: Moshe Sipper, "The Artificial Self-Replication Page," http://lslwww.epfl.ch/~moshes/selfrep/ or http://www.cs.bgu.ac.il/~sipper/selfrep/.
201. Moshe Sipper, James A. Reggia, "Go forth and replicate," Sci. Amer. 285(August 2001):34-43.
202. Simson Garfinkel, "Critique of nanotechnology," Whole Earth Review (Summer 1990):104.
203. David E.H. Jones, "Technical boundless optimism," Nature 374(27 April 1995):835-837; response: Ralph C. Merkle, "Nanocritics," 1995; http://www.zyvex.com/nanotech/nanocritics.html.

204. Gary Stix, "Trends in nanotechnology: waiting for breakthroughs," Sci. Amer. 274(April 1996):94-99; response: Ralph C. Merkle, "Foresight debate with Scientific American," 1996, http://www.foresight.org/SciAmDebate/SciAmResponse.html.
205. "Maxwell's Demon — A Predecessor of Nanotechnology," in Michael Gross, Travels to the Nanoworld: Miniature Machinery in Nature and Technology, Perseus Publishing, Cambridge, MA, 1999, pp. 211-214.
206. Theodore L. Brown, H. Eugene LeMay Jr., Bruce E. Bursten, Chemistry: The Central Science, 8th Edition, Prentice Hall, Upper Saddle River, NJ, 2000, pp. 199-200.
207. Ralph C. Merkle, "That's impossible! How good scientists reach bad conclusions," April 2001; http://www.zyvex.com/nanotech/impossible.html or http://www.foresight.org/impact/impossible.html.
208. K. Eric Drexler, Nanosystems: Molecular Machinery, Manufacturing, and Computation, John Wiley & Sons, New York, 1992; http://www.zyvex.com/nanotech/nanosystems.html.
209. Ralph C. Merkle, "Self-replicating systems and low cost manufacturing," in M.E. Welland, J.K. Gimzewski, eds., The Ultimate Limits of Fabrication and Measurement, Kluwer, Dordrecht, 1994, pp. 25-32; http://www.zyvex.com/nanotech/selfRepNATO.html.
210. Ralph C. Merkle, "Design-ahead for nanotechnology," in Markus Krummenacker, James Lewis, eds., Prospects in Nanotechnology: Toward Molecular Manufacturing, John Wiley & Sons, New York, 1995, pp. 23-52.
211. Ralph C. Merkle, "Self replicating systems and molecular manufacturing," J. Brit. Interplanet. Soc. 45(1992):407-413; http://www.zyvex.com/nanotech/selfRepJBIS.html.
212. Ralph C. Merkle, "Design considerations for an assembler," Nanotechnology 7(1996):210-215; http://www.zyvex.com/nanotech/nano4/merklePaper.html.
213. Ralph C. Merkle, "Convergent assembly," Nanotechnology 8(1997):18-22; http://www.zyvex.com/nanotech/convergent.html.
214. Ralph C. Merkle, "Binding sites for use in a simple assembler," Nanotechnology 8(1997):23-28; http://www.zyvex.com/nanotech/bindingSites.html.
215. Ralph C. Merkle, "A new family of six degree of freedom positional devices," Nanotechnology 8(1997):47-52; http://www.zyvex.com/nanotech/6dof.html.
216. Ralph C. Merkle, "A proposed 'metabolism' for a hydrocarbon assembler," Nanotechnology 8(1997):149-162; http://www.zyvex.com/nanotech/hydroCarbonMetabolism.html.
217. Ralph C. Merkle, "Casing an assembler," Nanotechnology 10(1999):315-322; http://www.zyvex.com/nanotech/casing.
218. Ralph C. Merkle, "Molecular building blocks and development strategies for molecular nanotechnology," Nanotechnology 11(2000):89-99; http://www.zyvex.com/nanotech/mbb/mbb.html.
219. Charles B. Musgrave, Jason K. Perry, Ralph C. Merkle, William A. Goddard III, "Theoretical studies of a hydrogen abstraction tool for nanotechnology," Nanotechnology 2(1991):187-195; http://www.zyvex.com/nanotech/Habs/Habs.html.
220. Charles W. Bauschlicher Jr., Alessandra Ricca, Ralph C. Merkle, "Chemical storage of data," Nanotechnology 8(1997):1-5.
221. Stephen P. Walch, Ralph C. Merkle, "Theoretical studies of diamond mechanosynthesis reactions," Nanotechnology 9(1998):285-296; http://www.iop.org/EJ/S/UNREG/T7WtMpSi4Oe3KKtSWopXsg/abstract/0957-4484/9/3/020. See also: S.P. Walch, W.A. Goddard III, R.C. Merkle, "Theoretical studies of reactions on diamond surfaces," Fifth Foresight Conference on Molecular Nanotechnology, 1997; http://www.foresight.org/Conferences/MNT05/Abstracts/Walcabst.html.
222. Jie Han, Al Globus, Richard Jaffe, Glenn Deardorff, "Molecular dynamics simulations of carbon nanotube-based gears," Nanotechnology 8(1997):95-102.
223. T. Cagin, A. Jaramillo-Botero, G. Gao, W.A. Goddard III, "Molecular mechanics and molecular dynamics analysis of Drexler-Merkle gears and neon pump," Nanotechnology 9(1998):143-152.
224. Al Globus, Charles W. Bauschlicher Jr., Jie Han, Richard L. Jaffe, Creon Levit, Deepack Srivastava, "Machine phase fullerene nanotechnology," Nanotechnology 9(1998):192-199; paper presented at the 5th Foresight Conference on Molecular Nanotechnology, November 1997; http://www.nas.nasa.gov/Groups/Nanotechnology/publications/1997/fullereneNanotechnology/.
225. J. Storrs Hall, "Architectural considerations for self-replicating manufacturing systems," Nanotechnology 10(1999):323-330; http://www.foresight.org/Conferences/MNT6/Papers/Hall/index.html or http://discuss.foresight.org/~josh/selfrepsys/index.html.
226. A. Globus, D. Bailey, J. Han, R. Jaffe, C. Levit, R.C. Merkle, D. Srivastava, "NASA applications of molecular nanotechnology," J. Brit. Interplanet. Soc. 51(1998):145-152; http://www.nas.nasa.gov/Groups/Nanotechnology/publications/1997/applications/.
227. Ralph C. Merkle, "It's a small, small, small, small world," Tech. Rev. (Feb/Mar 1997):25-; http://www.zyvex.com/nanotech/MITtecRvwSmlWrld/article.html.
228. Robert A. Freitas Jr., Nanomedicine, Volume I: Basic Capabilities, Landes Bioscience, Georgetown, TX, 1999; http://www.nanomedicine.com/NMI.htm.
229. Robert A. Freitas Jr., "Exploratory Design in Medical Nanotechnology: A Mechanical Artificial Red Cell," Artificial Cells, Blood Substitutes, and Immobil. Biotech. 26(1998):411-430; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9663339&dopt=Abstract (abstract); http://www.foresight.org/Nanomedicine/Respirocytes.html (paper). See also: Robert A. Freitas Jr., "Respirocytes: High Performance Artificial Nanotechnology Red Cells," Nanotechnology Magazine 2(October 1996):1, 8-13.
230. Robert A. Freitas Jr., "Clottocytes: Artificial Mechanical Platelets," Foresight Update No. 41, 30 June 2000, pp. 9-11; http://www.imm.org/Reports/Rep018.html or http://www.kurzweilai.net/meme/frame.html?main=/articles/art0460.html.
231. Robert A. Freitas Jr., "Say Ah!" The Sciences 40(July/August 2000):26-31; http://www.foresight.org/Nanomedicine/SayAh/index.html or http://www.kurzweilai.net/meme/frame.html?main=/articles/art0189.html.
232. Robert A. Freitas Jr., "Nanodentistry," J. Amer. Dent. Assoc. 131(November 2000):1559-1566; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11103574&dopt=Abstract (abstract), http://www.rfreitas.com/Nano/Nanodentistry.htm (paper).
233. Robert A. Freitas Jr., "Microbivores: Artificial Mechanical Phagocytes using Digest and Discharge Protocol," Zyvex preprint, March 2001; http://www.zyvex.com/Publications/articles/Microbivores.html. See also: "Microbivores: Artificial Mechanical Phagocytes," Foresight Update No. 44, 31 March 2001, pp. 11-13; http://www.imm.org/Reports/Rep025.html and http://www.kurzweilai.net/meme/frame.html?main=/articles/art0453.html.
234. Robert A. Freitas Jr., "Robots in the bloodstream: the promise of nanomedicine," Pathways, The Novartis Journal 2(October-December 2001):36-41; http://www.kurzweilai.net/meme/frame.html?main=/articles/art0410.html.
235. Robert A. Freitas Jr., Nanomedicine, Volume IIA: Biocompatibility, Landes Bioscience, Georgetown, TX, 2003; http://www.nanomedicine.com/NMIIA.htm.
236. Robert A. Freitas Jr., "Progress in Nanomedicine and Medical Nanorobotics," in Michael Rieth, Wolfram Schommers, eds., Handbook of Theoretical and Computational Nanotechnology, American Scientific Publishers, Stevenson Ranch, CA, 2005.
237. Stanislaw M. Ulam, Adventures of a Mathematician, Charles Scribner, New York, 1976, p. 32.
238. Stephen C. Kleene, Introduction to Metamathematics, D. van Nostrand, Princeton, NJ, 1952; Introduction to Mathematical Logic, John Wiley, New York, 1967; Formalized Recursive Functionals and Formalized Realizability, Memoirs, No. 1/89, American Mathematical Society, 1969.
239. Egon Borger, Computability, Complexity, Logic, Studies in the Foundations of Mathematics, Volume 128, North-Holland, Amsterdam, 1989; http://www.di.unipi.it/~boerger/cclbookcontents.html.
240. Michael Sipser, Introduction to the Theory of Computation, Chapter 6, First Edition, PWS Publishing Company, Albany, N.Y., 1997; http://www-math.mit.edu/~sipser/book.html.
241. Piergiorgio Odifreddi, Classical Recursion Theory, Volume II, North-Holland, Amsterdam, 1999.
242. W. Ross Ashby, "The self-reproducing system," in C.A. Muses, W.S. McCulloch, eds., Aspects of the Theory of Artificial Intelligence, Plenum Press, New York, 1962, pp. 9-18.
243. John G. Kemeny, "Man viewed as a machine," Sci. Amer. 192(April 1955):58-67; Sci. Amer. 192(June 1955):6 (errata).

244. Gottfried Wilhelm von Leibniz, The Monadology, 1698; translated by Robert Latta; http://www.orst.edu/instruct/phl302/texts/leibniz/monadology.html. Reprinted in: Gottfried Wilhelm von Leibniz, The Monadology and Other Philosophical Essays, Macmillan, New York, 1965; translated by Paul Schrecker and Anne Martin Schrecker.
245. G. Kampis, V. Csanyi, "Replication in abstract and natural systems," BioSystems 20(1987):143-152.
246. Margaret A. Boden, "Autopoiesis and life," Cognitive Science Quarterly 1(2000):117-145; http://www.dcs.shef.ac.uk/~amanda/boden.pdf.
247. Mary Shelley, Frankenstein, or The Modern Prometheus, Lackington, Hughes, Harding, Mavor, and Jones, London, 1818; http://home.tiscali.nl/~hamberg/Frankenstein/fulltext.html.
248. F. Thieberger, The Great Rabbi Loew of Prague: His Life and Work and the Legend of the Golem, Horovitz Publishing Co., London, 1955.
249. Rachel Strasser, "An anomalous Genesis: metaphor and implication in the creation of the golem," 1999; http://soda.csua.berkeley.edu/~ether/thesistext.html or http://www.csua.berkeley.edu/~ether/thesistext.html.
250. Julien Offray de La Mettrie, L'Homme Machine, d'Elie Luzac, Leyden, 1748. Translated as: Julien Offray de La Mettrie, Man a Machine, Open Court Publishing Company, La Salle, IL, 1912, 1943, 1961. Translated and revised by Mary Whiton Calkins. E-text at: http://humanum.arts.cuhk.edu.hk/humftp/E-text/La_Mettrie/machine.html. See also: Julien Offray de La Mettrie, Man a Machine and Man a Plant, Richard A. Watson et al, eds., Hackett, Indianapolis, 1994.
251. Baron d'Holbach (Paul Henri Thiry), Systeme de la nature, 1770. Paul Henri Thiry, Baron d'Holbach, The System of Nature, 2 vols (H.D. Robinson, ed.), Mendum, Boston MA, 1889. Baron d'Holbach, System of Nature, Franklin, New York, 1970; Garland Publ. Co., New York, 1984; Oxford University Press, Oxford, 1995; Clinamen Press Ltd., Manchester, U.K., 2000.
252. Pierre Jean George Cabanis, Rapports du physique et du moral de l'homme, 1796-1797. Pierre Jean George Cabanis, On the Relation Between the Physical and Moral Aspects of Man, 2 volumes translated by Margaret Duggan Saidi, edited by George Mora, The Johns Hopkins University Press, Baltimore MD, 1981.
253. Samuel Butler, Unconscious Memory, David Bogue, London, 1880. Reprinted as: Samuel Butler, Unconscious Memory: The Shrewsbury Edition of the Works of Samuel Butler, Volume 6, Classic Books, London, 1923; Jonathan Cape, London, 1924; pp. 13, 15.
254. Edward Pontee, "Karel Capek's R.U.R. (Rossum's Universal Robots): Background and Summary"; http://www.umich.edu/~engb415/literature/pontee/RUR/RURsmry.html.
255. Dennis G. Jerz, "R.U.R. (Rossum's Universal Robots)," 8 October 2002; http://www.uwec.edu/academic/curric/jerzdg/RUR/index.html.
256. Gloria McMillan, "Rossum's Universal Robots, With Link Documents," 2003; http://www.u.arizona.edu/%7Egmcmilla/capek.html.
257. Immanuel Kant, The Critique of Judgement, Part II Critique of Teleological Judgement, 1790; in R.M. Hutchins, M.J. Adler, transl. by James Creed Meredith, Britannica World Books, Vol. 42, 1952, pp. 550-613.
258. John Collier, "Organized Complexity: Properties, Models and the Limits of Understanding," http://www.nu.ac.za/undphil/collier/papers/cuba-complexity.pdf. See other papers at http://www.nu.ac.za/undphil/collier/papers.html.
259. Erik Benson, "Self-referential sentences," http://erikbenson.com/index.cgi?node=self-referential%20sentences.
260. D. Hofstadter, "Metamagical themas," Sci. Amer. 246(January 1982):12-17. Reprinted in: Douglas R. Hofstadter, Metamagical Themas: Questing for the Essence of Mind and Pattern, Bantam Books, New York, 1986.
261. Bhagavad-Gita, http://www.geocities.com/m_k_krishna_swamy/GitaByRajaji/introductory.htm or http://www.hindubooks.org/books_by_rajaji/bhagavad_gita/introductory/page6.htm; Charles T. Tart, "Chapter 11. Observation of Internal States," States of Consciousness, E.P. Dutton & Co., New York, 1975, pp. 156-162, http://www.druglibrary.org/special/tart/soc11.htm; Gertrude W. Van Pelt, Hierarchies: The Ladder of Life, Theosophical University Press, 1998, http://www.theosociety.org/pasadena/gdpmanu/hierarch/herarc-1.htm#infinte.
262. C.L. Nehaniv, Kerstin Dautenhahn, "Self-replication and reproduction: considerations and obstacles for rigorous definitions,", Proc. GWAL-98, 3rd German Workshop on Artificial Life 1998, Germany; Abstracting and Synthesizing the Principles of Life, Verlag Harri Deutsch, 1998; http://homepages.feis.herts.ac.uk/~comqkd/gwal-wg.ps.
263. Michael A. Arbib, "Some comments on self-reproducing automata," in John F. Hart, Satoru Takasu, eds., Systems and Computer Science, University of Toronto Press, Toronto, 1967, pp. 42-59.
264. John Maynard Smith, The Problems of Biology, Oxford University Press, Oxford, 1986.
265. Ian Stewart, "Why Have Sex?" The Sensual Magazine; from lecture given at Gresham College, London, on 11 February 1998; http://www.the-sensual-magazine.com/pages/features/whyhavesex.htm.
266. David J. Furley, Two Studies in the Greek Atomists, Princeton University Press, Princeton, NJ, 1967.
267. Ralph E. Kenyon, Jr., "Chapter V. Atomism And Divisionism After Aristotle. Epicurus (341-270 BC)," in Atomism and Infinite Divisibility, Ph.D. Dissertation, University of Massachusetts at Amherst, February 1994; http://www.xenodochy.org/rekphd/chapter5.html.
268. Bart J. Bok, "The Milky Way galaxy," Sci. Am. 244(March 1981):92-120, 115.
269. Bryant Adams, personal communication to Robert A. Freitas Jr., 10 September 2003.
270. P.L. Luisi, "About various definitions of life," Origins Life Evol. Biosphere 28(1998):613-622.
271. Foresight Institute, "Molecular Nanotechnology Guidelines: Draft Version 3.7," 4 June 2000; http://www.foresight.org/guidelines/.
272. Bryant Adams, Hod Lipson, "A Unifying Framework for Self-Replication Phenomena," Cornell University preprint, 2003, in review.
273. Ralph C. Merkle, Eric G. Parker, George D. Skidmore, "Method and system for self-replicating manufacturing stations," United States Patent No. 6,510,359, 21 January 2003; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,510,359.WKU.&OS=PN/6,510,359.
274. George Dyson, "Darwin Among the Machines; or, the Origins of [Artificial] Life," presentation for The Third Culture published in Edge 21, 8 July 1997; http://www.edge.org/3rd_culture/dyson/dyson_p6.html or http://www.edge.org/documents/archive/edge21.html.
275. Richard Dawkins, The Selfish Gene, Oxford University Press, New York, 1976.
276. Arun K. Pati, Samuel L. Braunstein, "Quantum mechanical universal constructor," Phys. Rev. Lett. (2003), submitted; online at arXiv:quant-ph/0303124v1, 19 March 2003, 7 pp; http://arxiv.org/PS_cache/quant-ph/pdf/0303/0303124.pdf.
277. Charles Seife, "Bad News for Quantum Clones," ScienceNOW, 7 May 2003; http://sciencenow.sciencemag.org/cgi/content/full/2003/507/1.
278. Michael A. Arbib, Brains, Machines, and Mathematics, Second Edition, Springer-Verlag, 1987.
300. Pierre Marchal, "John von Neumann: the founding father of artificial life," Artificial Life 4(Summer 1998):229-235.
301. John von Neumann biographies; see: http://www-groups.dcs.st-andrews.ac.uk/~history/Mathematicians/Von_Neumann.html;
http://ei.cs.vt.edu/~history/VonNeumann.html;
http://www.brunel.ac.uk:8080/depts/AI/alife/al-vonne.htm;
http://www.rit.edu/~drk4633/vonNeumann/;
http://www.rheingold.com/texts/tft/4.html;
http://www.physics.umd.edu/robot/neumann.html.
302. Herman H. Goldstine, The Computer from Pascal to von Neumann, Princeton University Press, NJ, 1972.
303. Sudarsana Srinivasan, "I'm Sterile — but My Robot's Not: John von Neumann's Self-Reproducing Automata's Moral Reflection in Philip K. Dick's 'Autofac'," STS-129: Artificial Life, Prof. Michael John Gorman, 15 November 2001; http://www.stanford.edu/class/sts129/essays/srinivasan2.htm.
304. Steve J. Heims, John von Neumann and Norbert Wiener: From Mathematics to the Technologies of Life and Death, MIT Press, Cambridge, MA, 1980.
305. M.A. Arbib, "Self-reproducing automata — some implications for theoretical biology," in C. H Waddington, ed., Towards a Theoretical Biology, 2. Sketches, Edinburgh University Press, 1969, pp. 204-226; 321-338 (notes on the Second Symposium).
306. Michael A. Arbib, Theories of Abstract Automata, Prentice-Hall, Englewood Cliffs, NJ, 1969.
307. W.S. McCulloch, W. Pitts, "A logical calculus of the ideas immanent in nervous activity," Bull. Math. Biophys. 5(1943):115-133.

308. Gianluca Tempesti, “A Self-Repairing Multiplexer-Based FPGA Inspired by Biological Processes,” Ph.D. thesis, 1998; http://lslwww.epfl.ch/pages/embryonics/thesis/.
309. John von Neumann, “Probabilistic logics and the synthesis of reliable organisms from unreliable components,” in C.E. Shannon, J. McCarthy, eds., Automata Studies, Princeton University Press, Princeton, NJ, 1956, pp. 43-98. (Also in Collected Works, Vol. 5, pp. 329-378.).
310. Alan Turing, “On computable numbers with an application to the Entscheidungs problem,” Proc. London Math. Soc. 42(1936):230-265. See also: R. Herken, ed., The Universal Turing Machine: A Half-Century Survey, Oxford University Press, Oxford, 1988.
311. M.A. Arbib, “From universal Turing machines to self-reproduction,” in R. Herken, ed., The Universal Turing Machine: A Half-Century Survey, Oxford University Press, Oxford, 1988, pp.177-189.
312. Barry McMullin, “What is a Universal Constructor?” Technical Report bmcm9301, School of Engineering, Dublin City University, May 1993; http://www.eeng.dcu.ie/~alife/bmcm9301/bmcm9301.pdf.
313. Barry McMullin, personal communication to Robert A. Freitas Jr., 14 October 2003.
314. Motoyosi Sugita, “Functional analysis of chemical systems in vivo using a logical circuit equivalent. V. Molecular biological interpretation of the self-reproducing automata theory and chemico-physical interpretation of information in biological systems,” J. Theor. Biol. 53(1975):223-237.
315. Antonia J. Jones, “Self-replicating probes for galactic exploration,” Department of Computing, Imperial College, London, 15 October 2000 (asserted to be notes from a lecture delivered at Cranfield and Imperial in 1991), 18 pp; http://www.cs.cf.ac.uk/user/Antonia.J.Jones/Lectures/Specials/SelfReplicatingAutomata.pdf.
316. V. Korogodin, V. Korogodina, Information as a Basis of Life, Phoenix, Moscow, 2000.
317. John von Neumann, “The general and logical theory of automata,” in L.A. Jeffress, ed., Cerebral Mechanisms in Behavior — The Hixon Symposium, John Wiley & Sons, New York, 1951, pp. 1-31. See also in A.H. Taub, ed., John von Neumann: Collected Works, Volume V: Design of Computers, Theory of Automata and Numerical Analysis, Pergamon Press, New York, 1963, pp. 288-329. (Slightly edited version of von Neumann’s paper that was read at the Hixon Symposium on 20 September 1948 in Pasadena, California.).
318. John von Neumann, “Re-evaluation of the Problems of Complicated Automata — Problems of Hierarchy and Evolution,” Fifth Lecture, University of Illinois, December 1949. Text of lecture reprinted in: John von Neumann, Theory of Self-Reproducing Automata, A.W. Burks, ed., University of Illinois Press, Urbana IL, 1966, pp. 74-87. Lecture notes also published in: W. Aspray, A. Burks, eds., Papers of John von Neumann on Computing and Computer Theory, MIT Press, Cambridge, MA, 1987, pp. 477-490.
319. A.G. Cairns-Smith, The Life Puzzle, University of Toronto Press, Toronto, 1971.
320. Hendrik Tiedemann, Jorg Heitkotter, “Theory of self-reproducing automata and life: : Foundation for a theoretical biology?” 20 December 1995, in prep. for J. Theor. Biol.; ftp://ftp.de.uu.net/pub/research/ci/Alife/zooland/online/al96.ps.gz or http://citeseer.nj.nec.com/update/81626.
321. John von Neumann, The Theory of Automata: Construction, Reproduction, Homogeneity, original unpublished manuscript, 1952-1953. Edited and reprinted in: John von Neumann, Theory of Self-Reproducing Automata, A.W. Burks, ed., University of Illinois Press, Urbana IL, 1966, pp. 91-381.
322. S. Ulam, “Random processes and transformations,” Proc. 1950 Intl. Congress on Mathematics, 2(1952):264-275 (American Mathematical Society, Providence, RI).
323. Ian Stewart, “Rules of Engagement,” New Scientist 159(29 August 1998):36-40; http://www.ams.org/new-in-math/mathdigest/199903-cellular.html (summary).
324. http://alife.santafe.edu/alife/topics/jvn/jvn.html.
325. Barry McMullin, “Artificial Knowledge: An Evolutionary Approach,” Ph.D. Dissertation, 1992; http://www.eeng.dcu.ie/~alife/bmcm_phd/.
326. John von Neumann, “Theory and Organization of Complicated Automata,” in William Aspray, Arthur Burks, eds., Papers of John von Neumann on Computing and Computer Theory, MIT Press, Cambridge, MA, 1987.
327. Richard Dawkins, The Extended Phenotype, W.H. Freeman, Oxford, 1982.
328. K. Eric Drexler, “Biological and nanomechanical systems: Contrasts in evolutionary capacity,” in Christopher G. Langton, ed., Artificial Life, Santa Fe Institute, Studies in the Science of Complexity, Volume VI, Addison-Wesley, New York, 1989, pp. 501-519.
329. W.M. Elsasser, The Physical Foundations of Biology, Pergamon Press, New York, 1958.
330. E.P. Wigner, “The probability of the existence of a self-reproducing unit,” in The Logic of Personal Knowledge: Essays presented to Michael Polanyi on his 70th birthday, The Free Press, Glencoe, IL, 1961, pp. 231-238.
331. S. Wolfram, Theory and Applications of Cellular Automata, World Scientific, Singapore, 1986.
332. Tommaso Toffoli, Norman Margolus, Cellular Automata Machines: A New Environment for Modeling, MIT Press, Cambridge, MA, 1987.
333. Andrew Adamatzky, Identification of Cellular Automata, Taylor & Francis, 1995.
334. Richard J. Gaylord, Kazume Nishidate, Modeling Nature: Cellular Automata Simulations With Mathematica, Springer-Verlag, New York, 1996.
335. Andrew Ilachinski, Cellular Automata: A Discrete Universe, World Scientific Publ. Co., 2001.
336. Stephen Wolfram, A New Kind of Science, Wolfram Media, Inc., 2002; http://www.wolframscience.com/.
337. Stephan Wolfram, “Cryptography with cellular automata,” Proc. Crypto ‘85, 1985, pp. 429-432.
338. H.H. Chou, J.A. Reggia, R. Navarro-Gonzalez, J. Wu, “An extended cellular space method for simulating autocatalytic oligonucleotides,” Computers in Chemistry 18(1994):33-43.
339. L. Edwards, Y. Peng, J.A. Reggia, “Computational models for the formation of protocell structures,” Artificial Life 4(1998):61-77.
340. A. Dorin, “Creating a physically-based, virtual-metabolism with solid cellular automata,” Artificial Life VII: Proceedings of the Seventh International Conference on Artificial Life, MIT Press, Cambridge, MA, 2000, pp. 13-20.
341. Naoaki Ono, Takashi Ikegami, “Selection of catalysts through cellular reproduction,” in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 57-64; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub2844.pdf.
342. Jaime Lagunez-Otero, Pedro Pablo Gonzalez Perez, Maura Cardenas-Garcia, Octavio Rosas, Armando Franyuti, “Cellulat,” in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 97-100; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub1665.pdf.
343. V.I. Goldanskii, V.V. Kuzmin, “Spontaneous mirror symmetry breaking in nature and the origin of life,” Z. Phys. Chemie. 269(1988):216-274.
344. Maarten Boerlijst, Pauline Hogeweg, “Self-structuring and selection: spiral waves as a substrate for prebiotic evolution,” in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 255-276.
345. K. Preston, Jr., M.J.B. Duff, S. Levialdi, Philip E. Norgren, Jun-Ichiro Toriwaki, “Basics of cellular logic with some applications in medical image processing,” Proc. IEEE 67(May 1979):826-856.
346. Alvy Ray Smith, “Simple nontrivial self-reproducing machines,” in C. Langdon, C. Taylor, J. Farmer, S. Rasmussen, eds., Artificial Life II, Addison-Wesley, New York, 1992, pp. 709-725.
347. E.F. Codd, Cellular Automata, Academic Press, New York, 1968.
348. James A. Reggia, Steven L. Armentrout, Hui-Hsien Chou, Yun Peng, “Simple systems that exhibit self-directed replication,” Science 259(26 February 1993):1282-1287.
349. J. Devore, R. Hightower, “The Devore variation of the Codd self-replicating computer,” 30 November 1992 draft paper, presented at the Third Workshop on Artificial Life, Santa Fe, New Mexico. Reported by John R. Koza, “Artificial life: spontaneous emergence of self-replicating and evolutionary self-improving computer programs,” in Christopher G. Langton, Artificial Life III, Proc. Volume XVII Santa Fe Institute Studies in the Sciences of Complexity, Addison-Wesley Publishing Company, New York, 1994, p. 260. (“Original work carried out in the 1970s though apparently never published.”[1287]).

350. J. Myhill, "The abstract theory of self-reproduction," in A.W. Burks, ed., Essays on Cellular Automata, University of Illinois Press, Urbana, IL, 1970, pp. 206-218.
351. J. Myhill, "Chapter 7," in M. Mesarovic, ed., Views on General Systems Theory, Krieger, Hunterington, New York, 1964.
352. Thomas J. Ostrand, "Pattern reproduction in tessellation automata of arbitrary dimension," J. Comput. Syst. Sci. 5(1971):623-628.
353. Edward F. Moore, "Machine models of self-reproduction," in R.E. Bellman, ed., Proceedings of the 14th Symposium in Applied Mathematics, American Mathematical Society, New York, 1962, pp. 17-33. Reprinted in A.W. Burks, ed., Essays on Cellular Automata, University of Illinois Press, Urbana, Illinois, 1970, pp. 187-203.
354. Michael A. Arbib, "Simple self-reproducing universal automata," Information and Control 9(1966):177-189.
355. A. Waksman, "A model of replication," J. ACM 16(1969):178-188.
356. J. Maddox, "Simulating the replication of life," Nature 305(1983):469.
357. Gabor T. Herman, "On universal computer-constructors," Information Processing Letters 2(1973):61-64.
358. Christopher G. Langton, "Self-reproduction in cellular automata," in J. Doyne Farmer, T. Toffoli, S. Wolfram, eds., Cellular Automata, Proceedings of an Interdisciplinary Workshop, 7-11 March 1983, Los Alamos, NM, North-Holland Physics Publishing, Amsterdam, 1983, pp. 135-144.
359. Christopher G. Langton, "Self-reproduction in cellular automata," Physica D 10(1984):135-144.
360. Christopher G. Langton, "Studying artificial life with cellular automata," Physica D 22(1986):120-149.
361. Christopher G. Langton, "Artificial Life," in C. Langton, ed., Artificial Life, SFI Studies in the Sciences of Complexity, Addison-Wesley Publ. Co., 1988, pp. 1-47. See also: http://necsi.org/postdocs/sayama/sdsr/java/.
362. J. Byl, "Self-reproduction in small cellular automata," Physica D 34(1989):295-299.
363. Robert Rosen, "On a logical paradox implicit in the notion of a self-reproducing automaton," Bull. Math. Biophys. 21(1959):387-394; Robert Rosen, "Letter to the editor: Self-reproducing automaton," Bull. Math. Biophys. 24(1962):243-245; Burton S. Guttman, "A resolution of Rosen's paradox for self-reproducing automata," Bull. Math. Biophys. 28(1966):191-194.
364. E.R. Banks, "Universality in Cellular Automata," IEEE Conference Record of 11th Annual Symposium on Switching and Automata Theory, Santa Monica, 28-30 October 1970, New York, IEEE, 1970, pp. 194-215.
365. Lutz Priese, "On a simple combinatorial structure sufficient for syblying nontrivial self-reproduction," J. Cybernetics 6(1976):101-137.
366. Steen Rasmussen, Carsten Knudsen, Rasmus Feldberg, Morten Hindsholm, "The Coreworld: emergence and evolution of cooperative structures in a computational chemistry," in S. Forrest, ed., Emergent Computation: Self-Organizing, Collective, and Cooperative Computing Networks, MIT Press, Cambridge, MA, 1990, pp. 111-134; also in Physica D 42(1990):111-134.
367. M. Sipper, G. Tempesti, D. Mange, E. Sanchez, "Special issue: Von Neumann's legacy: On self replication," Artificial Life 4(Summer 1998); http://www-mitpress.mit.edu/journal-issue-abstracts.tcl?issn=10645462&volume=4&issue=3.
368. Steen Rasmussen, Carsten Knudsen, Rasmus Feldberg, "Dynamics of programmable matter," in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley Publishing Company, Redwood City, CA, 1992, pp. 211-254.
369. Jason D. Lohn, James A. Reggia, "Discovery of self-replicating structures using a genetic algorithm," Proc. 1995 IEEE Intl. Conf. on Evolutionary Computation (ICEC'95), 1995, pp. 678-683; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/icec1995.pdf.
370. J.D. Lohn, "Automated discovery of self-replicating structures in cellular space automata models," Dept. of Computer Science Tech. Report CS-TR-3677, University of Maryland at College Park, August 1996; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/cs-tr-3677.pdf.
371. J.D. Lohn, J.A. Reggia, "Automatic discovery of self-replicating structures in cellular automata," IEEE Transactions on Evolutionary Computation 1(September 1997):165-178; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/tec1997.pdf.
372. John R. Koza, "Artificial life: spontaneous emergence of self-replicating and evolutionary self-improving computer programs," in Christopher G. Langton, Artificial Life III, Proc. Volume XVII Santa Fe Institute Studies in the Sciences of Complexity, Addison-Wesley Publishing Company, Reading, MA, 1994, pp. 225-262.
373. John R. Koza, James P. Rice, "Process for problem solving using spontaneously emergent self-replicating and self-improving entities," United States Patent No. 5,390,282, 14 February 1995; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,390,282.WKU.&OS=PN/5,390,282.
374. J. Ibanez, D. Anabitarte, I. Azpeitia, O. Barrera, A. Barrutieta, H. Blanco, F. Echarte, "Self-inspection based reproduction in cellular automata," in F. Moran, A. Moreno, J. J. Merelo, P. Chacon, eds., ECAL'95: Third European Conference on Artificial Life, Volume 929 of Lecture Notes in Computer Science, Springer-Verlag, Heidelberg, 1995, pp. 564-576.
375. Hiroki Sayama, "Artificial self-replication and evolution," New England Complex Systems Institute (NECSI); http://necsi.org/projects/sayama/artificial.html.
376. Eleonora Bilotta, Antonio Lafusa, Pietro Pantano, "Is self-replication an embedded characteristic of artificial/living matter?" in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 38-48; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub1967.pdf.
377. Gary William Flake, The Computational Beauty of Nature: Computer Explorations of Fractals, Chaos, Complex Systems, and Adaptation, MIT Press, Cambridge, MA, 2000.
378. M. Sipper, "Non-uniform cellular automata: Evolution in rule space and formation of complex structures," in R.A. Brooks, P. Maes, eds., Artificial Life IV, MIT Press, Cambridge, MA, 1994, pp. 394-399; http://lslwww.epfl.ch/~moshes/papers.html.
379. M. Sipper, "Studying artificial life using a simple, general cellular model," Artificial Life 2(Fall 1994):1-35; http://lslwww.epfl.ch/~moshes/papers.html.
380. Moshe Sipper, Evolution of Parallel Cellular Machines: The Cellular Programming Approach, Springer-Verlag, Heidelberg, 1997; http://lslwww.epfl.ch/~moshes/pcm.html.
381. J.A. Reggia, H.-H. Chou, J. D. Lohn, "Cellular automata models of self-replicating systems," in M. Zelkowitz, ed., Advances in Computers, Vol. 47, Academic Press, New York, 1998, pp. 141-183; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/aic1998.pdf.
382. Jason D. Lohn, "Cellular space models of self-replicating systems," Lect. Math. Life Sci. 26(1999):11-30.
383. Jason D. Lohn, James A. Reggia, "Exploring the design space of artificial self-replicating structures," in L.C. Jain, ed., Evolution of Engineering and Information Systems and Their Applications, CRC Press, 2000, pp. 67-103; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/jainchapter2000.pdf.
384. M. Sipper, Machine Nature: The Coming Age of Bio-Inspired Computing, McGraw-Hill, New York, 2002; http://www.moshesipper.com/mn/.
385. D.C. Bunzli, M.S. Capcarrere, "Fault-tolerant structures: towards robust self-replication in a probabilistic environment," in J. Kelemen, P. Sosik, eds., Advances in Artificial Life, Proc. 6th European Conf. (ECAL2001), Springer-Verlag, Berlin, 2001, pp. 90-99.
386. C.L. Nehaniv, "Evolution in Asynchronous Cellular Automata," Artificial Life VIII, MIT Press, 2002, pp. 65-73; http://parallel.hpc.unsw.edu.au/complex/alife8/proceedings/sub7376.pdf or http://homepages.feis.herts.ac.uk/~nehaniv/pubs.html.
387. J. Signorini, "How a SIMD machine can implement a complex cellular automaton? A case study: von Neumann's 29-state cellular automaton," in Supercomputing '89: Proceedings of the ACM/IEEE Conference, 1989, pp. 175-186.
388. Umberto Pesavento, "An implementation of von Neumann's self-reproducing machine," Artificial Life 2(Summer 1995):337-354. See also: R. Nobili, U. Pesavento, "John von Neumann's Automata Revisited," 1994, described by W.R. Buckley as "an unpublished manuscript detailing an investigation into cellular automata based on von Neumann's specification, and also cellular automata based on a variation to the state set on the von Neumann specification." Online animations of the von Neumann constructor and other cell automata, based on the Pesavento/Nobili work, are online at: Tim Hutton, "John von Neumann's Universal Constructor," http://www.eastman.ucl.ac.uk/~thutton/Evolution/JvN/ or at http://alife.santafe.edu/alife/software/jvn.html.
389. A.R. Smith, III, "Cellular automata and formal languages," IEEE Conference Record of 11th Annual Symposium on Switching and Automata Theory, Santa Monica, 28-30 October 1970, New York, IEEE, 1970, pp. 216-224.

390. Martin Gardner, "The fantastic combinations of John Conway's new solitaire game 'life'," Sci. Amer. 223(October 1970):120-123.
391. Martin Gardner, "On cellular automata, self-reproduction, the Garden of Eden and the game 'Life'," Sci. Amer. 224(February 1971):112-117.
392. Justin Milliun, Judy Reardon, Peter Smart, "Life with your computer," Byte 3(December 1978):45-50; David J. Buckingham, "Some facts of Life," Byte 3(December 1978):54-67; Jonathan Millen, "One-dimensional Life," Byte 3(December 1978):68-74; William Englander, "Programming quickies: Life," Byte 3(December 1978):76-82; Mark D. Niemiac, "Life algorithms," Byte 4(January 1979):90-97; Randy Soderstrom, "Life can be easy," Byte 4(April 1979):166-169; Selby Evans, "APL makes Life easy (and vice versa)," Byte 5(October 1980):192-193.
393. Elwyn R. Berlekamp, John Horton Conway, Richard Guy, Winning Ways for Your Mathematical Plays, Academic Press, New York, 1982.
394. Martin Gardner, Wheels, Life, and Other Mathematical Amusements, W.H. Freeman, New York, 1983.
395. William Poundstone, The Recursive Universe, Morrow, New York, 1985.
396. A.K. Dewdney, "Computer Recreations: The game of Life acquires some successors in three dimensions," Sci. Amer. 256(February 1987):16-24.
397. Bastien Chopard, Michel Droz, Cellular Automata Modeling of Physical Systems, Cambridge University Press, 1998.
398. R. Rucker, J. Walker, "Origins of CelLab. Classical era: Von Neumann to Gosper," Cellular Automata Laboratory, http://www.fourmilab.ch/cellab/manual/chap5.html; movie of 3-D version of the Fredkin Parity rule, http://www.fourmilab.ch/cellab/manual/footnote.html#F5_7; see also http://wwwmaths.anu.edu.au/DoM/firstyear/poetry/ArtificialLife/AL2__Self_reproduction(6).pdf.
399. Tim Hutton, personal communication to Robert A. Freitas Jr., 13 August 2003, including a quotation from a letter written to Hutton by Nobili; Nobili's contribution is also mentioned in the README file for the original code at http://www.eastman.ucl.ac.uk/~thutton/Evolution/JvN/jvn.readme.
400. Animations of self-replicating loops: http://necsi.org/postdocs/sayama/sdsr/java/.
401. Hui-Hsien Chou, James A. Reggia, "Emergence of self-replicating structures in a cellular automata space," Physica D 110(15 December 1997):252-272.
402. James A. Reggia, Jason D. Lohn, Hui-Hsien Chou, "Self-replicating structures: evolution, emergence, and computation," Artificial Life 4(Summer 1998):283-302; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/alife1998.pdf. See also: Hui-Hsien Chou, "A demo of artificial life," http://www.complex.iastate.edu/hhchou/research_ca_demo1.html.
403. Hiroki Sayama, "Constructing Evolutionary Systems on a Simple Deterministic Cellular Automata Space," Ph.D. Dissertation, Department of Information Science, Graduate School of Science, University of Tokyo, 1998.
404. Hiroki Sayama, "Introduction of structural dissolution into Langton's self-reproducing loop," in C. Adami, R.K. Belew, H. Kitano, C.E. Taylor, eds., Artificial Life VI: Proc. 6th Intl. Conf. on Artificial Life, MIT Press, Cambridge, MA, 1998, pp. 114-122.
405. Hiroki Sayama, "A new structurally dissolvable self-reproducing loop evolving in a simple cellular automata space," Artificial Life 5(Fall 1999):343-365; http://mitpress.mit.edu/journals/ARTL/Sayama.pdf.
406. SDSR Loop webpage: "Structurally Dissolvable Self-Reproducing Loop & Evoloop: Evolving SDSR Loop," NECSI, 17 August 2000; http://necsi.org/postdocs/sayama/sdsr/.
407. C. Bennett, "The thermodynamics of computation — a review," Intl. J. Theoret. Phys. 21(1981):905-940; Charles H. Bennett, Rolf Landauer, "The fundamental physical limits of computation," Sci. Amer. 253(July 1985):48-56; R. Landauer, "Energy Requirements in Computation," Appl. Phys. Lett. 51(1987):2056-2058; R. Landauer, "Dissipation and noise immunity in computation and communication," Nature 335(1988):779-784; C.H. Bennett, "Notes on the history of reversible computation," IBM J. Res. Dev. 32(1 January 1988):16-23; R.C. Merkle, "Reversible electronic logic using switches," Nanotechnology 4(1993):21-40; J. Storrs Hall, "Nanocomputers and reversible logic," Nanotechnology 5(1994):157-167.
408. K. Morita, K. Imai, "Self-reproduction in a reversible cellular space," Theoretical Computer Science 168(1996):337-366.
409. Katsunobu Imai, Takahiro, Kenichi Morita, "Self-reproduction in three-dimensional reversible cellular space," Artificial Life 8(Spring 2002):155-174; http://mitpress.mit.edu/catalog/item/default.asp?sid=2AC0A07D-41B4-44CE-AB40-CAA5E0D78F32&ttype=6&tid=8860 (abstract).
410. K. Morita, K. Imai, "A simple self-reproducing cellular automaton with shape-encoding mechanism," in C. Langton, T. Shimohara, eds., Artificial Life V: Proceedings of the Fifth International Workshop on the Synthesis and Simulation of Living Systems, MIT Press, Cambridge, MA, 1997.
411. K. Morita, K. Imai, "Logical universality and self-reproduction in reversible cellular automata," in T. Higuchi, M. Iwata, W. Liu, eds., Proceedings of The First International Conference on Evolvable Systems: From Biology to Hardware (ICES96), Volume 1259 of Lecture Notes in Computer Science, Springer-Verlag, Heidelberg, 1997, pp. 152-166.
412. J.-L. Beuchat, J.-O. Haenni, "Von Neumann's 29-state cellular automaton: A hardware implementation." IEEE Transactions on Education 43(August 2000):300-308; http://ieeexplore.ieee.org/iel5/13/18732/00865206.pdf.
413. G. Tempesti, "A new self-reproducing cellular automata capable of construction and computation," in F. Moran, A. Moreno, J.J. Merelo, P. Chacon, eds., Advances in Artificial Life, Proc. 3rd European Conf. on Artificial Life (ECAL '95), Vol. 929, Springer-Verlag, 1995, pp. 555-563.
414. C.L. Nehaniv, "Self-Reproduction in Asynchronous Cellular Automata," NASA/DoD Conference on Evolvable Hardware (15-18 July 2002, Alexandria, Virginia, USA), IEEE Computer Society Press, 202, pp. 201-209, 2002; available at http://homepages.feis.herts.ac.uk/~nehaniv/pubs.html.
415. Daniel Mange, Andre Stauffer, Enrico Petraglio, Gianluca Tempesti, "Artificial Cell Division," Fifth International Workshop on Information Processing in Cells and Tissues (IPCAT 2003), Workshop Pre-Proceedings, Swiss Federal Institute of Technology, Lausanne, 2003, pp. 257-274.
416. Daniel Mange, Andre Stauffer, Enrico Petraglio, Gianluca Tempesti, "Self-replicating loop with universal construction," submitted to Elsevier Preprint, 12 September 2003.
417. Alvy Ray Smith, "Cellular Automata Theory," Ph.D. Thesis, Technical Report No. 2, Digital Systems Laboratory, Stanford University, Stanford CA, 1969; "Simple computational-universal cellular spaces," J. ACM 18(1971):339-353.
418. Douglas R. Hofstadter, Godel, Escher, Bach: An Eternal Golden Braid, Basic Books, New York, 1979, p. 504-513.
419. Michael J. Apter, Cybernetics and Development, Pergamon Press, Oxford, 1966, Chapter 5.
420. Paul Bratley, Jean Millo, "Computer recreations: self-reproducing programs," Software Practice and Experience 2(1972):397-400.
421. Louise Hay, "Self-reproducing programs," Creative Computing 6(July 1980):134-136.
422. John Burger, David Brill, Filip Machi, "Self-reproducing programs," Byte 5(August 1980):72, 74.
423. Daniel Weise, "Thlef-reproduthing programth," Byte 5(December 1980):16, 18.
424. William Sommerfeld, "Self-replicating code," Byte 6(March 1981):16, 18.
425. Gary P. Thompson, "The Quine Page"; http://www.nyx.net/~gthompso/quine.htm.
426. David Madore, "A page about quines," 13 December 2002; http://www.eleves.ens.fr:8080/home/madore/computers/quine.html.
427. Craig S. Kaplan, "Self-Referential Programs," http://www.cgl.uwaterloo.ca/~csk/washington//paper/toc.html; Phil Scovis, "Self-Replicating Programs," http://home.att.net/~phildonnics/Phil/PJP/Quine/.
428. A.K. Dewdney, "Computer Recreations: In a game called Core War hostile programs engage in a battle of bits," Sci. Amer. 250(May 1984):14-22.
429. A.K. Dewdney, "Computer Recreations: A Core War bestiary of viruses, worms and other threats to computer memories," Sci. Amer. 252(March 1985):14-23; http://www.skrenta.com/cloner/sci-am.html.
430. A.K. Dewdney, "Computer Recreations: A program called MICE nibbles its way to victory at the first Core War tournament," Sci. Amer. 256(January 1987):14-20.
431. A.K. Dewdney, The Armchair Universe, W.H. Freeman, New York, 1988.
432. A.K. Dewdney, "Of worms, viruses and core war," Sci. Amer. 260(March 1989):90-93; http://www.koth.org/info/akdewdney/Last.htm.
433. John F. Shoch, Jon A. Hupp, "The 'worm' programs: early experience with a distributed computation," Commun. ACM 25(1982):172-180.
434. Eugene H. Spafford, "The internet worm: crisis and aftermath," CACM 32(1989):678-687.

435. Katie Hafner, John Markoff, Cyberpunk, Simon and Schuster, New York, 1991.
436. Hiroki Sayama, “Self-Replicating Worms That Increase Structural Complexity through Gene Transmission,” 2000; http://www.necsi.org/postdocs/sayama/./worms/sayamaAL7.ps.gz. See also: H. Sayama, Self-Replicating Worms Website; http://complex.hc.uec.ac.jp/sayama/worms/.
437. Jose Nazario, “The future of internet worms,” paper presented at the Blackhat Briefings, Las Vegas, 20 July 2001; http://www.crimelabs.net/docs/worm.html.
438. A.K. Dewdney, “Computer Recreations: Sharks and fish wage an ecological war on the toroidal planet Wa-Tor,” Sci. Amer. 251(June 1984):14-22.
439. A.K. Dewdney, “Computer Recreations: Exploring the field of genetic algorithms in a primordial computer sea full of Flibs,” Sci. Amer. 253(May 1985):21-32.
440. Walter R. Stahl, “Self-reproducing automata,” Perspect. Biol. Med. 8(Spring 1965):373-393.
441. Walter R. Stahl, “A model of self-reproduction based on string-processing finite automata,” in H.H. Pattee E.A. Edelsack, Louis Fein, A.B. Callahan, eds., Natural Automata and Useful Simulations, Spartan Books, Washington, DC, 1966, pp. 43-72.
442. Thomas S. Ray, “Is it alive or is it GA?” in R. Belew, L. Booker, eds., Proc. Fourth Intl. Conf. On Genetic Algorithms, Morgan Kaufmann, San Mateo, CA, 1991, pp. 527-534; John Travis, “Electronic ecosystem,” Science News 140(10 August 1991):88-90; Thomas S. Ray, “An approach to the synthesis of life,” in C. G. Langton, C. Taylor, J. D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 371-408; Thomas S. Ray, “An evolutionary approach to synthetic biology: Zen and the art of creating life,” Artificial Life 1(1994):179-209; Thomas S. Ray, “Evolving complexity,” Artificial Life and Robotics 1(1997):21-26; Thomas S. Ray, Joseph Hart, “Evolution of differentiated multi-threaded digital organisms,” in C. Adami, R. Belew, H. Kitano, C.Taylor, eds., Proc. of Artificial Life VI, MIT Press, Cambridge, MA, 1998, pp. 295-304; see website at: http://www.hip.atr.co.jp/~ray/tierra/tierra.html.
443. Thomas S. Ray, “Evolution, complexity, entropy and artificial reality,” Physica D 75(1994):239-263; http://www.isd.atr.co.jp/~ray/pubs/oji/ojihtml.html.
444. Tim Taylor, From Artificial Evolution to Artificial Life, Ph.D. thesis, University of Edinburgh, 1999; http://computing.tay.ac.uk/timtaylor/papers/thesis/html/main.html.
445. Nils Aall Barricelli, “Symbiogenetic evolution processes realized by artificial methods,” Methodos IX(1957):1-40.
446. Nils Aall Barricelli, “Numerical testing of evolution theories. Part I. Theoretical introduction and basic tests,” Acta Biotheoretica XVI(1962):69-98.
447. Nils Aall Barricelli, “Numerical testing of evolution theories. Part II. Preliminary tests of performance. Symbiogenesis and terrestrial life,” Acta Biotheoretica XVI(1963):99-126. See Taylor’s summary of Barricelli’s work at: http://computing.tay.ac.uk/timtaylor/papers/thesis/html/node39.html.
448. L.J. Fogel, A.J. Owens, M.J. Walsh, Artificial Intelligence Through Simulated Evolution, Wiley, New York, 1966.
449. Walter R. Stahl, “A computer model of cellular self-reproduction,” J. Theor. Biol. 14(1967):187-205.
450. Jon Reed, Robert Toombs, Nils Aall Barricelli, “Simulation of biological evolution and machine learning. I. Selection of self-reproducing numeric patterns by data processing machines, effects of hereditary control, mutation type and crossing,” J. Theor. Biol. 17(1967):319-342.
451. Gordon Pask, “The computer-simulated development of populations of automata,” Mathematical Biosciences 4(1969):101-127.
452. Michael Conrad, H.H. Pattee, “Evolution experiments with an artificial ecosystem,” J. Theor. Biol. 28(1970):393-409.
453. Nils Aall Barricelli, “Numerical testing of evolution theories,” J. Statist. Comput. Simul. 1(1972):97-127.
454. John H. Holland, “Studies of the spontaneous emergence of self-replicating systems using cellular automata and formal grammars,” in A. Lindenmayer, G. Rozenberg, eds., Automata, Languages, Development, North-Holland Publishing Co., New York, 1976, pp. 385-404.
455. Francisco J. Varela, Humberto R. Maturana, R. Uribe, “Autopoiesis: The organization of living systems, its characterization and a model,” BioSystems 5(1974):187-196.
456. Milan Zeleny, “Self-organization of living systems: A formal model of autopoiesis,” International Journal of General Systems 4(1977):13-28.
457. Barry McMullin, Francisco J. Varela, “Rediscovering computational autopoiesis,” in P. Husbands, I. Harvey, eds., Fourth European Conference on Artificial Life, MIT Press/Bradford Books, 1997, pp. 38-47; http://www.eeng.dcu.ie/~alife/bmcm-ecal97/ or http://www.eeng.dcu.ie/~alife/bmcm-ecal97/bmcm-ecal97.html.
458. Norman H. Packard, “Evolving bugs in a simulated ecosystem,” in Christopher G. Langton, ed., Artificial Life, Studies in the Sciences of Complexity, Santa Fe Institute, Volume VI, Addison-Wesley, New York, 1989, pp. 141-156.
459. Michael Travers, “Animal construction kits,” in Christopher G. Langton, ed., Artificial Life, Studies in the Sciences of Complexity, Santa Fe Institute, Volume VI, Addison-Wesley, New York, 1989, pp. 421-442.
460. C.E. Taylor, L. Muscatine, D.R. Jefferson, “Maintenance and breakdown of the Hydra-Chlorella symbiosis: A computer model,” Proc. Roy. Soc. Lond. B 238(1989):277-289.
461. David Jefferson, Robert Collins, Claus Cooper, Michael Dyer, Margot Flowers, Richard Korf, Charles Taylor, Alan Wang, “Evolution as a theme in artificial life: the Genesys/Tracker system,” in C. G. Langton, C. Taylor, J. D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 549-578; Robert J. Collins, David R. Jefferson, “AntFarm: Towards simulated evolution,” in C. G. Langton, C. Taylor, J. D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 579-601.
462. Jakob Skipper, “The computer zoo — evolution in a box,” in F.J. Varela, P. Bourgine, eds., Toward a Practice of Autonomous Systems: Proceedings of the First European Conference on Artificial Life, MIT Press, Cambridge, MA, 1992, pp. 355-364.
463. Chris Adami, C. Titus Brown, “Evolutionary learning in the 2-D artificial life system ‘Avida’,” in R. Brooks, P. Maes, eds., Artificial Life IV, MIT Press, Cambridge, MA, 1994, pp. 377-381; http://dllab.caltech.edu/pubs/. See also: “Avida Software,” Digital Life Laboratory; http://dllab.caltech.edu/avida/.
464. Larry Yaeger, “Computational genetics, physiology, metabolism, neural systems, learning, vision and behavior or poly-world: Life in a new context,” in C.G. Langton, ed., Artificial Life III, Volume XVII of Santa Fe Institute Studies in the Sciences of Complexity, Addison-Wesley, New York, 1994, pp. 263-298.
465. Lawrence Bull, Terence C. Fogarty, “Artificial symbiogenesis,” Artificial Life 2(Spring 1995):269-292.
466. David B. Fogel, Evolutionary Computation: Toward a new philosophy of machine intelligence, IEEE Press, Piscataway, NJ, 1995.
467. Chisato Numaoka, “Symbiosis and co-evolution in animats,” in F. Moran, A. Moreno, J.J. Merelo, P. Chacon, eds., Advances in Artificial Life: Third European Conference on Artificial Life, Lecture Notes in Artificial Intelligence, Springer-Verlag, New York, pp. 261-272.
468. A.N. Pargellis, “The spontaneous generation of digital ‘life’,” Physica D 91(1996):86-96; A.N. Pargellis, “The evolution of self-replicating computer organisms,” Physica D 98(1996):111-127. See also: Toby Howard, “Soup opera,” Personal Computer World Magazine, August 1996; http://www.cs.man.ac.uk/aig/staff/toby/writing/PCW/life.htm.
469. Mark A. Bedau, Emile Snyder, C. Titus Brown, Norman H. Packard, “A comparison of evolutionary activity in artificial evolving systems and in the biosphere,” in P. Husbands, I. Harvey, eds., Fourth European Conference on Artificial Life, MIT Press/Bradford Books, 1997, pp. 124-134.
470. Florent de Dinechin, “Self-replication in a 2-D von Neumann architecture,” in P. Husbands, I. Harvey, eds., Fourth European Conference on Artificial Life, MIT Press/Bradford Books, 1997, pp. 560-565.
471. David B. Fogel, ed., Evolutionary Computation: The Fossil Record, IEEE Press, New York, 1998.
472. Ariel Dolan, The New Artificial Life (Alife) Database; http://www.aridolan.com/ad/adb/adtop.html.
473. Christoph Adami, Introduction to Artificial Life, Springer-Verlag, New York, 1998.

474. Karl Sims, “Evolving virtual creatures,” Siggraph ‘94 Proceedings, July 1994, pp.15-22; http://www.genarts.com/karl/papers/siggraph94.pdf.
475. Karl Sims, “Evolving 3-D morphology and behavior by competition,” in R. Brooks, P. Maes, eds., Artificial Life IV: Proceedings Fourth Intl. Workshop on the Synthesis and Simulation of Living Systems, MIT Press, Cambridge, MA, 1994, pp. 28-39; http://www.genarts.com/karl/papers/alife94.pdf.
476. Maciej Komosinski, Szymon Ulatowski, “FRAMSTICKS. Artificial Life for real people,” Poznan University of Technology; http://www.frams.poznan.pl/.
477. Steven Levy, Artificial Life, Vintage Books/Random House, New York, 1992, pp. 34-42.
478. Claus Emmeche, The Garden in the Machine: The Emerging Science of Artificial Life, Princeton University Press, Princeton, NJ, 1994. See also: C. Emmeche, “Life as an abstract phenomenon: Is Artificial Life possible?” in F. Varela, P. Bourgine, eds., Toward a Practice of Autonomous Systems, Proc. First European Conf. on Artificial Life, MIT Press, 1992.
479. Norman H. Packard, Mark A. Bedau, “Artificial life,” in Encyclopedia of Cognitive Science, Macmillan, New York, 2000, pp. 209-215; http://www.reed.edu/~mab/papers/ECS.pdf.
480. S. Rasmussen, “Bridging nonliving and living matter,” Paper S5-1, Proceedings of the Seventh International Symposium on Artificial Life and Robotics (AROB 7th ‘02); http://arob.cc.oita-u.ac.jp/AROB2002/7thHome.html.
481. Arnold Smith, Peter Turney, Robert Ewaschuk, “Self-replicating machines in continuous space with virtual physics,” Artificial Life 9(Winter 2003):21-40; http://mitpress.mit.edu/catalog/item/default.asp?sid=397A4A74-A9EC-4075-BCAB-BD971F891B0E&ttype=6&tid=10632 (abstract) and http://cogprints.ecs.soton.ac.uk/archive/00002888/ (paper) or http://arxiv.org/ftp/cs/papers/0304/0304022.pdf (NRC-44969 paper); Arnold Smith, Peter Turney, Robert Ewaschuk, “JohnnyVon: Self-replicating automata in continuous two-dimensional space,” NRC Technical Report ERB-1099, National Research Council of Canada, 2002; http://cogprints.ecs.soton.ac.uk/archive/00002440/ or http://extractor.iit.nrc.ca/johnnyvon/ERB-JohnnyVon.pdf. See also: “JohnnyVon: Self-Replicating Automata in Continuous Two-Dimensional Space,” arxiv.org/abs/cs.NE/0212010; JohnnyVon source code, Java applet and movies available at http://purl.org/net/johnnyvon/; Kimberly Patch, “Virtual DNA replicates,” Technology Research News, 26 February 2003; http://www.trnmag.com/Stories/2003/022603/Virtual_DNA_replicates_022603.html; and Mike Martin, “Machines that reproduce may be reality,” NewsFactor Network, 10 July 2003; http://www.newsfactor.com/perl/story/21893.html.
482. G. Yedid, G. Bell, “Macroevolution simulated with autonomously replicating computer programs,” Nature 420(19-26 December 2002):810-2, 756-757 (comment).
483. Steven Levy, Artificial Life, Vintage Books/Random House, New York, 1992.
484. Mark Ward, Virtual Organisms: The Startling World of Artificial Life, St. Martin’s Press, 2000.
485. Peter Bentley, Digital Biology, Simon and Schuster, New York, 2002.
486. Fred Cohen, “Computer viruses: theory and experiments,” Computers and Security 6(1987):22-35.
487. Fred B. Cohen, A Short Course on Computer Viruses, 2nd Edition, John Wiley, New York, 1994.
488. Allen Lundell, Virus! The Secret World of Computer Invaders That Breed and Destroy, Contemporary Books, Chicago, 1989.
489. Peter J. Denning, Computers Under Attack: Intruders, Worms and Viruses, ACM Press, Addison-Wesley Publ. Co., Reading, MA, 1990.
490. Harold Joseph Highland, ed., Computer Virus Handbook, Elsevier Advanced Technology, Oxford, 1990.
491. Lance J. Hoffman, ed., Rogue Programs: Viruses, Worms, and Trojan Horses, Van Nostrand Reinhold, New York, 1990.
492. David J. Stang, Computer Viruses, Second Edition, National Computer Security Association, Washington DC, 1990.
493. Eugene H. Spafford, “Computer viruses — a form of artificial life?” in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, Santa Fe Institute Studies in the Sciences of Complexity, Volume X, Addison-Wesley, Redwood City, CA, 1992, pp. 727-745.
494. Philip E. Fites, Peter Johnston, Martin Kratz, Computer Virus, Second Edition, Diane Publishing Co., 1999.
495. David Harley, Urs E. Gattiker, Robert Slade, Viruses Revealed, Osborne McGraw-Hill, New York, 2001.
496. J.P. Crutchfield, K. Young, “Inferring statistical complexity,” Phys. Rev. Lett. 63(1989):105-108.
497. Ming Li, Paul Vitanyi, An Introduction to Kolmogorov Complexity and Its Applications, Springer-Verlag, New York, 1993.
498. John Bates, Harvey Shepard, “Measuring complexity using information fluctuation,” Phys. Lett. A 172(1993):416-425.
499. M. Gell-Mann, S. Lloyd, “Information measures, effective complexity and total information,” Complexity 2(1996):44-52; M. Gell-Mann, “What is complexity?” Complexity 1(1995):16-19.
500. Remo Badii, Antonio Politi, Complexity: Hierarchical Structure and Scaling in Physics, Cambridge University Press, 1997.
501. Bruce Edmonds, Hypertext Bibliography of Measures of Complexity, last updated 3 July 1997; http://bruce.edmonds.name/combib/.
502. Bruce Edmonds, Syntactic Measures of Complexity, Ph.D. Dissertation, University of Manchester, 1999; http://bruce.edmonds.name/thesis/.
503. Christof Adami, “What is complexity?” BioEssays 24(2002):1085-1094; http://www.krl.caltech.edu/~adami/BE2002.pdf.
504. Christof Adami, Charles Ofria, Travis C. Collier, “Evolution of biological complexity,” Proc. Nat. Acad. Sci. (USA) 97(26 May 2000):4463-4468; http://xxx.lanl.gov/PS_cache/physics/pdf/0005/0005074.pdf.
505. Johan Chu, Christof Adami, “Propagation of information in populations of self-replicating code,” in C.G. Langton, T. Shimohara, eds., Proc. of Artificial Life V, Nara (Japan), 16-18 May 1996, MIT Press, Cambridge, MA, 1997, pp. 462-469; http://xxx.lanl.gov/PS_cache/adap-org/pdf/9605/9605001.pdf.
506. R.E. Lenski, C. Ofria, T.C. Collier, C. Adami, “Genome complexity, robustness, and genetic interactions in digital organisms,” Nature 400(1999):661-664; http://dllab.caltech.edu/pubs/nature99/.
507. Charles Ofria, Christoph Adami, Travis C. Collier, Grace K. Hsu, “Evolution of differentiated expression patterns in digital organisms,” Lect. Notes Artif. Intell. 1674(1999):129-138. Also published in D. Floreano et al, eds., Advances in Artificial Life, 5th European Conference (ECAL’99), 1999; http://xxx.lanl.gov/PS_cache/physics/pdf/0002/0002054.pdf.
508. I. Harvey, “Creatures from another world,” Nature 400(1999):618-619.
509. D. Wagenaar, C. Adami, “Influence of chance, history, and adaptation on evolution in Digitalia,” in M.A. Bedau, J.S. McCaskill, N.H. Packard, S. Rasmussen, eds., Proc. Artificial Life VII, MIT Press, Cambridge, MA, 2000, pp. 216-220.
510. H. Suzuki, “Evolution of self-reproducing programs in a core propelled by parallel protein execution,” Artificial Life 6(2000):103-108.
511. G. Yedid, G. Bell, “Microevolution in an electronic microcosm,” Am. Nat. 157(2001):465-487.
512. C.O. Wilke, J.L. Wang, C. Ofria, R.E. Lenski, C. Adami, “Evolution of digital organisms at high mutation rate leads to survival of the flattest,” Nature 412(19 July 2001):331-333; http://dllab.caltech.edu/pubs/nature01/.
513. C. Adami, “Ab initio modeling of ecosystems with artificial life,” Natural Resource Modeling 15(2002):133-146; http://arxiv.org/PS_cache/physics/pdf/0209/0209081.pdf.
514. H. Thimbleby, S.O. Anderson, P. Cairns, “A Framework for Modeling Trojans and Computer Virus Infection,” Computer Journal 41(July 1999):444–458. See also: H. Thimbleby, S.O. Anderson, P. Cairns, “Reply to ‘Comment on “A Framework for Modeling Trojans and Computer Virus Infection”‘ by E. Makinen,” Computer Journal 44(April 2001):324-325.
515. “Download virus definitions,” Symantec, 16 May 2003; http://securityresponse.symantec.com/avcenter/download.html.
516. Harold Thimbleby, “Computer Viruses,” Lecture at Gresham College, London, 21 March 2002; http://www.gresham.ac.uk/geometry/2001-2002/Lect210302.htm. Lecture notes revised from: H. Thimbleby, I.H. Witten, “Virus, Computer,” in A. Ralston, E.D. Reilly, D. Hemmendinger, eds., The Encyclopaedia of Computer Science, 4th edition, Nature Publishing Group, 2000, pp. 1839-1841.
517. Aleph Null, “Computer Recreations,” Software — Practice and Experience 2(January-March 1972):93-96.
518. David Gerrold, When Harlie Was One, Ballantine Books, New York, 1972.
519. John Brunner, The Shockwave Rider, Ballantine Books, New York, 1975.
520. G.J. Chaitin, Algorithmic Information Theory, Cambridge University Press, Cambridge, 1987.

521. J.R. Koza, Genetic Programming, MIT Press, Cambridge, MA, 1992.
522. Erik Schultes, "An instance of a replicator," in Christopher G. Langton, Artificial Life III, Proc. Volume XVII Santa Fe Institute Studies in the Sciences of Complexity, Addison-Wesley Publishing Company, New York, 1994, p. 1.
523. Andrew Whitaker, Viral Marketing in a Week, Hodder & Stoughton, 2003; Russell Goldsmith, Viral Marketing: Get Your Audience to Do Your Marketing for You, Pearson Professional Education, 2002; Ralph F. Wilson, "The six simple principles of viral marketing," Web Marketing Today, Issue 70, 1 February 2000, http://www.wilsonweb.com/wmt5/viral-principles.htm; Steve Jurvetson, Tim Draper, "Viral Marketing," Netscape M-Files, 1997, also in Business 2.0, November 1998, http://www.dfj.com/files/viralmarketing.html; "Viral Marketing," http://www.marketingterms.com/dictionary/viral_marketing/.
524. D.R. Hofstadter, "On Viral Sentences and Self-Replicating Sentences," Scientific American (January 1983):14-19. Reprinted in: Douglas R. Hofstadter, Metamagical Themas: Questing for the Essence of Mind and Pattern, Basic Books, 1985.
525. Richard Dawkins, "Chapter 11. Memes," The Selfish Gene, Oxford University Press, New York, 1976; Richard Brodie, Virus of the Mind, Integral Press, Seattle WA, 1996.
526. Susan Blackmore, Richard Dawkins, The Meme Machine, Oxford University Press, 2000; Douglas Rushkoff, Media Virus: Hidden Agendas in Popular Culture, Ballantine Books, New York, 1996.
527. L.M. Boyd column, "The men behave much the same," The Sun, Flagstaff, Arizona, Tuesday, 3 April 1984, p. 16.
528. David Moser, "This Is The Title Of This Story, Which Is Also Found Several Times In The Story Itself," Whole Earth Review, Fall 1990; http://www.triplette.com/by_david_moser.htm.
529. G. Taubes, "After 50 years, self-replicating silicon," Science 277(26 September 1997):1936.
530. Hector Fabio Restrepo, "Implementation of a Self-Replicating Universal Turing Machine," Ph.D. Dissertation, Thesis 2457, EPFL, 2001; http://lslwww.epfl.ch/pages/publications/rcnt_theses/restrepo/abstract.pdf (abstract) and http://lslwww.epfl.ch/pages/publications/rcnt_theses/restrepo/restrepo_thesis.pdf (thesis). See also: H.F. Restrepo, D. Mange, M. Sipper, "A self-replicating universal Turing machine: From von Neumann's dream to new embryonic circuits," in M.A. Bedau, J.S. McCaskill, N.H. Packard, S. Rasmussen, eds., Artificial Life VII, Proc. 7th Intl. Conf. on Artificial Life, MIT Press, Cambridge, MA, 2000.
531. D. Mange, A. Stauffer, "Introduction to embryonics: Towards new self-repairing and self-reproducing hardware based on biological-like properties," in N.M. Thalmann, D. Thalmann, eds., Artificial Life and Virtual Reality, John Wiley, England, 1994, pp. 61-72.
532. P. Marchal, C. Piguet, D. Mange, A. Stauffer, S. Durand, "Embryological development on silicon," in R.A. Brooks, P. Maes, eds., Artificial Life IV, MIT Press, Cambridge, MA, 1994, pp. 365-370.
533. D. Mange, M. Goeke, D. Madon, A. Stauffer, G. Tempesti, S. Durand, "Embryonics: A new family of coarse-grained field-programmable gate array with self-repair and self-reproducing properties," in E. Sanchez, M. Tomassini, eds., Towards Evolvable Hardware, Volume 1062 of Lecture Notes in Computer Science, Springer-Verlag, Heidelberg, 1996, pp. 197-220.
534. P. Marchal, P. Nussbaum, C. Piguet, S. Durand, D. Mange, E. Sanchez, A. Stauffer, G. Tempesti, "Embryonics: The birth of synthetic life," in E. Sanchez, M. Tomassini, eds., Towards Evolvable Hardware, Volume 1062 of Lecture Notes in Computer Science, Springer-Verlag, Heidelberg, 1996, pp. 166-196.
535. M. Sipper, D. Mange, A. Stauffer, "Ontogenetic hardware," BioSystems 44(1997):193-207.
536. D. Mange, D. Madon, A. Stauffer, G. Tempesti, "Von Neumann revisited: A Turing machine with self-repair and self-reproduction properties," Robotics and Autonomous Systems 22(1997):35-58.
537. Gianluca Tempesti, Daniel Mange, Andre Stauffer, "Self-replicating and self-repairing multicellular automata," Artificial Life 4(Summer 1998):259-282.
538. D. Mange, E. Sanchez, A. Stauffer, G. Tempesti, P. Marchal, C. Piguet, "Embryonics: A new methodology for designing field-programmable gate arrays with self-repair and self-replicating properties," IEEE Transactions on VLSI Systems 6(September 1998):387-399.
539. D. Mange, M. Sipper, P. Marchal, "Embryonic electronics," Biosystems 51(1999):145-152.
540. D. Mange, M. Sipper, A. Stauffer, G. Tempesti, "Towards robust integrated circuits: the Embryonics approach," Proc. IEEE 88(April 2000):516-541.
541. Lucian Prodan, Gianluca Tempesti, Daniel Mange, Andre Stauffer, "Embryonics: Electronic stem cells," in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. p101-105; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub2089.pdf.
542. G. Tempesti, D. Mange, E. Petraglio, A. Stauffer, Y. Thoma, "Developmental Processes in Silicon: An Engineering Perspective," Proc. 2003 NASA/DoD Conference on Evolvable Hardware (EH-2003), IEEE Computer Society Press, Los Alamitos, CA, 2003, pp. 255-264.
543. Andre Stauffer, Moshe Sipper, "Introduction: Interactive self-replication," in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 53-56; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub2756.pdf.
544. BioWall at EPFL website: http://lslwww.epfl.ch/biowall/. See also: C. Teuscher, D. Mange, A. Stauffer, G. Tempesti, "Bio-inspired computing tissues: Towards machines that evolve, grow, and learn," IPCAT'2001, 24 April 2001; http://lslwww.epfl.ch/~cteusche/download/papers/teuscher01_ipcat01.pdf.
545. Andre Stauffer, Moshe Sipper, "An interactive self-replicator implemented in hardware," Artificial Life 8(Spring 2002):175-183; http://mitpress.mit.edu/catalog/item/default.asp?sid=2AC0A07D-41B4-44CE-AB40-CAA5E0D78F32&ttype=6&tid=8861 (abstract).
546. Gianluca Tempesti, Christof Teuscher, "Biology Goes Digital," Xcell Journal 47(Fall 2003):40-45; http://www.xilinx.com/publications/xcellonline/xcell_47/xc_biowall47.htm.
547. George Musser, "Robot, heal thyself," Sci. Amer. 265(August 2001):40-41.
548. M.B. Hastings, C.J. Olson Reichhardt, C. Reichhardt, "Ratchet cellular automata," Phys. Rev. Lett. 90(2003):247004; http://xxx.lanl.gov/abs/cond-mat/0211302.
549. John Timler, Craig S. Lent, "Maxwell's demon and quantum-dot cellular automata," J. Appl. Phys. 94(2003):1050.
550. Lisa J.K. Durbeck, Nicholas J. Macias, "The Cell Matrix^{TM}: an architecture for nanocomputing," Nanotechnology 12(September 2001):217-230; http://www.cellmatrix.com/entryway/products/pub/ForesightIOP.pdf.
551. Michael Butts, Andr DeHon, Seth Copen Goldstein, "Molecular Electronics: Devices, Systems and Tools for Gigagate, Gigabit Chips," International Conference on Computer-Aided Design (ICCAD'02), November 2002; http://www.cs.caltech.edu/research/ic/pdf/tutorial_iccad2002.pdf.
552. James M. Tour, Long Cheng, David P. Nackashi, Yuxing Yao, Austen K. Flatt, Sarah K. St. Angelo, Thomas E. Mallouk, Paul D. Franzon, "NanoCell electronic memories," J. Am. Chem. Soc. 125(29 October 2003):13279-13283. See also: Jade Boyd, "NanoCells can function as key part of computer chips," Rice News 13(23 October 2003), http://www.riceinfo.rice.edu/projects/reno/rn/20031023/nanocells.html; and "Self-Assembled Nanocells Function As Non-Volatile Memory," 20 October 2003; http://www.sciencedaily.com/releases/2003/10/031020053847.htm.
553. Claus O. Wilke, Christoph Adami, "The biology of digital organisms," Trends in Ecology & Evolution 17(2002):528-532; http://www.krl.caltech.edu/~adami/TREE2002.pdf.
554. J. Maynard Smith, "Byte-sized evolution," Nature 335(1992):772-773.
555. Peter Turney, personal communication to Robert A. Freitas Jr., 5-7 August 2003.
556. Richard Laing, "The capabilities of some species of artificial organisms," J. Cybernetics 3(April-June 1973):16-25.
557. Richard A. Laing, "Some alternative reproductive strategies in artificial molecular machines," J. Theor. Biol. 54(1975):63-84.
558. Richard A. Laing, "Machines as organisms: An exploration of the relevance of recent results," BioSystems 11(1979):201-215.
559. Richard A. Laing, "Artificial molecular machines: a rapprochement between kinematic and tessellation automata," Proc. Intl. Symp. On Uniformly Structured Automata and Logic, Tokyo, 1975, pp. 73-80.

560. Richard A. Laing, "Automaton introspection," J. Comp. System Sci. 13(October 1976):172-183.

561. Richard A. Laing, "Automaton models of reproduction by self-inspection," J. Theor. Biol. 66(1977):437-456.

562. Richard A. Laing, "Automaton self-reference," dissertation, State University of New York, Binghampton, University Microfilms, Ann Arbor, MI, Publication No. TSZ 78-05, 542, 1978.

563. Richard A. Laing, "Anomalies of self-description," Synthese 38(1978):373-387.

564. Takashi Ikegami, Takashi Hashimoto, "Active mutation in self-reproducing networks of machines and tapes," Artificial Life 2(Spring 1995):305-318.

565. James Thatcher, "Universality in the von Neumann cellular model," in A.W. Burks, ed., Essays on Cellular Automata, University of Illinois Press, Urbana, Illinois, 1970, pp. 132-186.

566. C.Y. Lee, "A Turing Machine which prints its own code script," in Mathematical Theory of Automata, Polytechnic Press, Brooklyn, New York, 1963, pp. 155-164.

567. James Thatcher, "The construction of a self-describing Turing Machine," in Mathematical Theory of Automata, Polytechnic Press, Brooklyn, New York, 1963, pp. 165-171.

568. John Case, "Machine Self-Reference," Dept. of Computer and Information Sciences, University of Delaware, 21 April 2000; http://www.cis.udel.edu/~case/self-ref.html. See also: John Case, "A note on degrees of self-describing Turing machines," J. ACM 18(1971):329-338; John Case, "Periodicity in generations of automata," Mathematical Systems Theory 8(1974):15-32; John Case, "Infinitary self reference in learning theory," J. Exp. Theor. Artif. Intell. 6(1994):3-16.

569. Gregory A. Riccardi, "The independence of control structures in abstract programming systems," J. Comput. Syst. Sci. 22(1981):107-143.

570. James S. Royer, "A connotational theory of program structure," Lecture Notes in Computer Science, Vol. 273, Springer-Verlag, 1987; http://www.cis.syr.edu/people/royer/ps/index.html. See also: James S. Royer, John Case, Subrecursive Programming Systems: Complexity and Succinctness, Birkhauser, Boston, 1994.

571. Sanjay Jain, Daniel Osherson, James S. Royer, Arun Sharma, Systems That Learn, Second Edition, MIT Press, Cambridge, MA, 1999; http://www.cis.syr.edu/people/royer/stl2e/index.html.

572. Chris Phoenix, personal communication to Robert A. Freitas Jr., 26 September 2003.

573. George Friedman, personal communication to Robert A. Freitas Jr., 1 August 2003 and 2 October 2003.

574. Peter Silcox, personal communication to Robert A. Freitas Jr., 5 August 2003.

575. John Holland, "Chapter 8," in Adaptation in Natural and Artificial Systems, University of Michigan Press, Ann Arbor, MI, 1975.

576. George D. Skidmore, Eric Parker, Matthew Ellis, Neil Sarkar, Ralph Merkle, "Exponential assembly," paper presented at the 8th Foresight Conference, Washington DC, November 2000; http://www.foresight.org/Conferences/MNT8/Papers/Skidmore/index.html and http://www.zyvex.com/Publications/papers/exponentialGS.html. See also: "Exponential Assembly", 25 September 2001; http://www.zyvex.com/Research/exponential.html.

577. P. Husbands, I. Harvey, "Evolution versus design: Controlling autonomous robots," Proceedings of the Third Annual Conference on Artificial Intelligence, Simulation and Planning, IEEE Press, 1992, pp. 139-146.

578. I. Harvey, P. Husbands, D. Cliff, "Issues in evolutionary robotics," in J.A. Meyer, H. Roitblat, S. Wilson, eds., From Animals to Animats 2, MIT Press, Cambridge, MA, 1993, pp. 364-373.

579. D. Cliff, I. Harvey, H.P., "Explorations in evolutionary robotics," Adaptive Behavior 2(1993):73-110.

580. M. Mataric, D. Cliff, "Challenges in evolving controllers for physical robots," Robotics and Autonomous Systems, Special Issue of Evolutional Robotics 19(1996):67-83.

581. P. Husbands, J.A. Meyer, eds., Evolutionary Robotics: First European Workshop, EvoRobot98, Springer-Verlag, 1998.

582. Sevan G. Ficici, Richard A. Watson, Jordan B. Pollack, "Embodied evolution: A response to challenges in evolutionary robotics," in Jeremy L. Wyatt, John Demiris, eds., Eighth European Workshop on Learning Robots, 1999, pp. 14-22; http://demo.cs.brandeis.edu/papers/ewlr8.pdf.

583. Jordan B. Pollack, Hod Lipson, Pablo Funes, Sevan G. Ficici, Greg Hornby, "Coevolutionary robotics," in John R. Koza, Adrian Stoica, Didier Keymeulen, Jason Lohn, eds., First NASA/DoD Workshop on Evolvable Hardware (EH'99), Pasadena, CA, 19-21 July 1999, IEEE Press, 1999; http://demo.cs.brandeis.edu/papers/nasa_eh99.pdf.

584. Pablo Funes, Jordan Pollack, "Computer evolution of buildable objects," in P. Husbands, I. Harvey, eds., Fourth European Conference on Artificial Life, MIT Press, Cambridge, MA, 1997, pp. 358-367; http://demo.cs.brandeis.edu/papers/ecal97.pdf and http://demo.cs.brandeis.edu/papers/other/cs-97-191.html.

585. Pablo Funes, Jordan Pollack, "Evolutionary body building: Adaptive physical designs for robots," Artificial Life 4(Autumn 1998):337-357; http://demo.cs.brandeis.edu/papers/funpolalife.pdf.

586. Pablo J. Funes, Jordan B. Pollack, "Componential structural simulator," Brandeis University Department of Computer Science, Technical Report CS-98-198, 1998; http://demo.cs.brandeis.edu/papers/cs98-198.pdf.

587. Pablo Funes, Jordan Pollack, "Computer evolution of buildable objects," in P. Bentley, ed., Evolutionary Design by Computers, Morgan Kaufmann, San Francisco, 1999, pp. 387-403; http://demo.cs.brandeis.edu/papers/edc98.pdf.

588. Jordan B. Pollack, Hod Lipson, Sevan G. Ficici, Pablo Funes, Gregory S. Hornby, Richard A. Watson, "Evolutionary techniques in physical robotics," in J. Miller, ed., Evolvable Systems: From Biology to Hardware, Proc. of the Third Intl. Conf. (ICES 2000), Springer, 2000, pp. 175-186 (Lecture Notes in Computer Science, Vol. 1801); http://demo.cs.brandeis.edu/papers/ices00.pdf.

589. Gregory S. Hornby, Hod Lipson, Jordan B. Pollack, "Evolution of generative design systems for modular physical robots," IEEE Intl. Conf. on Robotics and Automation, 2001; http://demo.cs.brandeis.edu/papers/hornby_icra01.pdf.

590. Jordan B. Pollack, Hod Lipson, Pablo Funes, Gregory Hornby, "First three generations of evolved robots," EvoRobots 2001, pp. 62-71.

591. G.S. Hornby, H. Lipson, J.B. Pollack, "Generative representations for the automated design of modular physical robots," IEEE Trans. Robotics and Automation 19(2003):703-719.

592. Jordan B. Pollack, Hod Lipson, Sevan G. Ficici, Pablo Funes, Greg Hornby, Richard A. Watson, "Evolutionary techniques in physical robotics," in Peter J. Bentley, David W. Corne, eds., Creative Evolutionary Systems, Morgan-Kaufmann, San Francisco, 2001, pp. 511-524.

593. Stefano Nolfi, Dario Floreano, Evolutionary Robotics: The Biology, Intelligence, and Technology of Self-Organizing Machines, MIT Press, Cambridge, MA, 2000.

594. Richard A. Watson, Sevan G. Ficici, Jordan B. Pollack, "Embodied evolution: Embodying an evolutionary algorithm in a population of robots," 1999 Congress on Evolutionary Computation, IEEE Press, 1999, pp. 335-342; http://demo.cs.brandeis.edu/papers/ee_cec99.pdf; Richard A. Watson, Sevan G. Ficici, Jordan B. Pollack, "Embodied evolution: Distributing an evolutionary algorithm in a population of robots," Technical Report CS-00-208, 2000; http://demo.cs.brandeis.edu/papers/ee_journal.pdf.

595. G.M. Werner, M.G. Dyer, "Evolution of communication in artificial organisms," in C. Langton, C. Taylor, J. Farmer, S. Rasmussen, eds., Artificial Life II, Addison-Wesley, 1991, pp. 659-687.

596. J. Ventrella, "Attractiveness vs. efficiency (how mate preference affects locomotion in the evolution of artificial swimming organisms)," in C. Adami, R. Belew, H. Kitano, C. Taylor, eds., Artificial Life VI, MIT Press, Cambridge, MA, 1998, pp. 178-186.

597. Walter Fontana, "Algorithmic chemistry," in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 159-209.

598. Walter Fontana, Gunter Wagner, Leo W. Buss, "Beyond digital naturalism," Artificial Life 1(1994):211-227.

599. W. Fontana, L.W. Buss, "What would be conserved if 'the tape were played twice'?" Proc. Natl. Acad. Sci. (USA) 91(18 January 1994):757-761.

600. H. Lund, J. Hallam, W. Lee, "Evolving robot morphology," Proc. 4th IEEE Intl. Conf. on Evolution, IEEE Press, 1997; H. Lund, J. Hallam, W. Lee, "A hybrid gp/ga approach for co-evolving controllers and robot bodies to achieve fitness-specified tasks," Proc. Third IEEE Intl. Conf. on Evolutionary Computation, IEEE Press, 1997.

601. Gerald Joyce, personal communication to Robert A. Freitas Jr., 27 August 2003.
602. Tom Johnson, Self-Similar Melodies, 75 rue de la Roquette, 75011 Paris, 1996, pp. 233-277. See also: Tom Johnson, "Self-Replicating Loops," http://homepage.mac.com/javiruiz/Articles/selfreplicatingloops.html; David Feldman, "Review of Self-Similar Melodies by Tom Johnson," Leonardo Music Journal 8(1999):80-84, http://kalvos.org/johness2.html.
603. T. Kaga, T. Fukuda, "Group behaviour control on dynamically reconfigurable robotic system," Intl. J. Syst. Sci. 32(March 2001):353-363.
650. Charles Michael Collins, "Self reproducing fundamental fabricating machines (F-Units)," United States Patent No. 5,659,477, 19 August 1997; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,659,477.WKU.&OS=PN/5,659,477.
651. Charles M. Collins, "Self Reproducing Fundamental Fabricating Machine System," United States Patent No. 5,764,518, 9 June 1998; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,764,518.WKU.&OS=PN/5,764,518.
652. John Iovine, Robots, Androids and Animatrons, Second Edition: 12 Incredible Projects You Can Build, 2nd edition, McGraw-Hill/TAB Electronics, New York, 2001; http://www.amazon.com/exec/obidos/tg/detail/-/0071376836/.
653. Stan Gibilisco, Teach Yourself Electricity and Electronics, 3rd edition, McGraw-Hill/TAB Electronics, New York, 2001, p. 663; http://www.amazon.com/exec/obidos/tg/detail/-/0071377301/.
654. Second International Conference on Evolvable Systems: From Biology to Hardware (ICES98), 23-25 September 1998, Swiss Federal Institute of Technology, Lausanne, Switzerland; http://lslwww.epfl.ch/ices98/.
655. Patricia S. Warrick, Mind in Motion: The Fiction of Philip K. Dick, Southern Illinois University Press, Carbondale, IL, 1987.
656. Philip K. Dick, Vulcan's Hammer: Battle of the Brain Machines, Ace Books, New York, 1960.
657. Karel Capek, R.U.R. (Rossum's Universal Robots). A Play in Three Acts and an Epilogue. Written in Czech in 1920; premiered in Prague in early 1921 and first performed in New York in 1922; translated from the Czech by Paul Selver and adapted for the English Stage by Nigel Playfair, then first published in English translation in 1923 by Humphrey Milford, Oxford University Press, London, 1923 and by Doubleday, Page & Company, Garden City, New York, 1923; reprinted by Dover Publications, New York, 2001, and by Players Press Inc., 2002.
658. Edmond Hamilton, "The Metal Giants," Weird Tales, December 1926. See cover art at http://www.vintagelibrary.com/used/pulps/bobw0037.jpg.
659. S. Fowler Wright, "Automata," Weird Tales, September 1929.
660. Laurence Manning, "The Call of the Mech-Men," Wonder Stories, November 1933.
661. Clifford D. Simak, "How-2," Galaxy, November 1954. See cover art at http://www.sciencefictionmuseum.com/classics/stories/gc5411a.html.
662. A.E. Van Vogt, The Voyage of the Space Beagle, Simon & Schuster, New York, 1950; Collier Books, reprint edition, 1992.
663. A.E. van Vogt, "Automaton," Other Worlds, September 1950.
664. Lord Edward Dunsany, The Last Revolution, Jerrolds, London & New York, 1951.
665. Philip K. Dick, "The Gun," Planet Stories, September 1952. Reprinted in: The Collected Stories of Philip K. Dick, Volume One: Beyond Lies the Wub, Underwood-Miller, 1987, pp. 35-46.
666. Philip K. Dick, "Second Variety," Space Science Fiction, May 1953. (Manuscript received at Scott Meredith Literary Agency on 3 October 1952.). Also available in: Philip K. Dick, Second Variety and Other Classic Stories by Philip K. Dick, Citadel Press, 1991.
667. Bertrand Russell, "Dr. Southport Vulpes' Nightmare," in Bertrand Russell, Nightmares of Eminent Persons and Other Stories, Allen & Unwin, 1954 and Spokesman Press, 2000.
668. Philip K. Dick, "Autofac," Galaxy Science Fiction Magazine 16(November 1955); Philip K. Dick, The Collected Stories of Philip K. Dick, Volume 4: The Minority Report, Citadel Press, 1992, pp. 1-20; pp. 1-6 excerpted online at http://www.amazon.com/exec/obidos/tg/detail/-/0806512768. See additional excerpt at: http://www.polyamory.org/~howard/Nanotechnology/Autofac.html.
669. Poul Anderson, "Epilogue," Analog 69(March 1962):112-158.
670. Stanislaw Lem, The Invincible, Wydawnietwo Literakie, Krakow, 1964. English translation copyright 1973 by Charter Communications, Inc. Stanislaw Lem, The Invincible, The Seabury Press, 1973; Stanislaw Lem, The Invincible, Penguin Books, Harmondsworth, Middlesex, 1976 (trans. Wendayne Ackerman) and Ace Books, 1976.
671. Fred Saberhagen, Berserker, Ballantine Books, New York, 1967; Fred Saberhagen, Berserker, Ace Books, New York, 1980, 1984, 1992. See also Berserker website at http://www.berserker.com/FredsBerserkers.html.
672. John Thomas Sladek, The Reproductive System, Gollancz, London, 1968; John Thomas Sladek, Mechasm, Ace Books, New York, 1969 and Pocket Books, New York, 1980; John Sladek, The Reproductive System, Orion Publishing Group, 2000 and Victor Gollancz, 2001. Review at http://www.crescentblues.com/5_2issue/bk_sladek_reproduction.shtml.
673. Fred Saberhagen, Brother Assassin, Ace Books, New York, 1969; Fred Saberhagen, Brother Berserker, Orion Publishing Co., 1989. See cover art at http://www.berserker.com/bk_brotherassassin.htm.
674. Ilya Varshavsky, "Homunculo (Homunculus)," 1967.
675. Bruce Sterling, "Taklamakan," in Bruce Sterling, A Good Old-Fashioned Future, Bantam Spectra, New York, 1999.
676. David Zindell, The Broken God, Spectra, 1995, p. 271; http://www.amazon.com/exec/obidos/tg/detail/-/0553762168/.
677. Edward F. Moore, "Artificial living plants," Sci. Amer. 195(October 1956):118-126.
678. Iben Browning, "Organization and Vistas of the Entirety: A Periodic Table," Report No. 98-001, Research Division, Bell Aircraft Corporation, December 1956. Reprinted in: Nelson B. Winkless III, Iben Browning, Robots on Your Doorstep: A Book About Thinking Machines, Robotics Press, Portland, 1978, pp. 13-36.
679. Nelson B. Winkless III, Iben Browning, Robots on Your Doorstep: A Book About Thinking Machines, Robotics Press, Portland, 1978.
680. L.S. Penrose, R. Penrose, "A self-reproducing analogue," Nature 179(8 June 1957):1183; http://www.aeiveos.com/~bradbury/Authors/Computing/Penrose-LS/ASRA.html.
681. L.S. Penrose, "Mechanics of self-reproduction," Ann. Human Genetics 23(November 1958):59-72.
682. L.S. Penrose, "Automatic mechanical self-reproduction," New Biology 28(January 1959):92-117.
683. L.S. Penrose, "Self-reproducing machines," Sci. Amer. 200(June 1959):105-114.
684. L.S. Penrose, "Developments in the theory of self-replication," New Biology 31(1960):57-66.
685. L.S. Penrose, "On living matter and self-replication," in Irving John Good, Alan James Mayne, John Maynard Smith, eds., The Scientist Speculates, Heinemann, London, 1962; Capricorn Books Edition, New York, 1965, pp. 258-271.
686. L.S. Penrose, "Automatic mechanical self-replication," 16 mm kodachrome movie film, Hemel Hempstead, Herts., England, filmed and distributed by H.A. Cresswell, 1958; 11 minutes. Cited in: Edward F. Moore, "Machine models of self-reproduction," Proc. Symp. Applied Math. 14(1962):17-33; and in Michael J. Apter, Cybernetics and Development, Pergamon Press, Oxford, 1966.
687. Homer Jacobson, "On models of reproduction," American Scientist 46(September 1958):255-284.
688. Harold J. Morowitz, "A model of reproduction," American Scientist 47(June 1959):261-263.
689. Charles R. Morgan, "Terraforming with nanotechnology," J. Brit. Interplanet. Soc. 47(1994):311-318.
690. M.D. Nussinov, S.V. Lysenko, V.V. Patrikeev, "Terraforming of Mars through terrestrial microorganisms and nanotechnological devices," J. Brit. Interplanet. Soc. 47(1994):319-320.
691. Robert J. Coppinger, "The Drexlerian Terraformation of Mars: A New Ark for Humanity," Newsletter of the Molecular Manufacturing Shortcut Group, Volume 4, Number 1, First Quarter, 1996; http://www.islandone.org/MMSG/9601-news.html#RTFToC53.
692. Stephen L. Gillett, "Inward Ho!" Chapter 4, in Stanley Schmidt, Robert Zubrin, eds., Islands in the Sky: Bold New Ideas for Colonizing Space, John Wiley & Sons, 1996, pp. 71-84; http://www.amazon.com/exec/obidos/tg/detail/-/0471135615/.
693. Arthur C. Clarke, 2010: Odyssey Two, Random House, New York, 1982.
694. James Patrick Hogan, Code of the Lifemaker, Ballantine Del Rey, New York, 1983; Baen Books, New York, 2002; see "Background" at http://www.jamesphogan.com/books/codelife/background.shtml?ballantine95.

695. Greg Bear, The Forge of God, Gollancz, New York, 1987; http://www.wikipedia.org/wiki/The_Forge_of_God (brief summary). See also: Greg Bear, Anvil of Stars, Century, London, U.K., 1992; http://postviews.editthispage.com/books/byTitle/AnvilOfStars (review).
696. Frederick Pohl, Mars Plus, Baen Books, New York, 1994.
697. George Parsons Lathrop, "In the Deep of Time," English Illustrated Magazine, March 1897, pp. 47-72. Reprinted in George W. Locke, Worlds Apart: An Anthology of Interplanetary Fiction, Cornmarket Reprints, 1972.
698. J.A.N. Lee, "Konrad Zuse — Part II," 30 September 1994; http://ei.cs.vt.edu/~history/Zuse.2.html.
699. M.E. Merchant, "The future of batch manufacture," Phil. Trans. Royal Soc. Lond. A 275(1973):357-372.
700. David Nitzan, Charles A. Rosen, "Programmable Industrial Automation," IEEE Trans. Comp. C-25(December 1976):1259-1270.
701. Fujio Honda, ed., "Methodology for unmanned metal working factory," Project Committee of Unmanned Manufacturing System Design, Bulletin of Mechanical Engineering Laboratory No. 13, Tokyo, 1974.
702. T. Ohmi, M. Kanai, F. Honda, "Research and development of a flexible manufacturing system complex provided with laser — a Japanese National Project," paper presented at the Workshop on Flexible Manufacturing Systems, 11-14 September 1978, Peoria, IL.
703. James A. Albus, People's Capitalism: The Economics of the Robot Revolution, New World Books, College Park, Maryland, 1976.
704. "Robots to produce robots at Fujitsu," handout from an English-language newspaper at the IAF Conference in Tokyo, 21-28 September 1980.
705. William Chapman, "Japanese open offensive for technological gains with robot development," The Washington Post, Monday, 13 October 1980, p. A38.
706. Kathleen K. Wiegner, "The dawn of battle," Forbes 128(26 October 1981):77-79.
707. Kuni Sadamoto, ed., Robots in The Japanese Economy, Survey Japan, Tokyo, 1981.
708. M.E. Merchant, "Production: A dynamic challenge," IEEE Spectrum (May 1983):36-39.
709. UPI, "Japanese Welcome Blue-Collar Robotry: Machines Make Machines to Make Machines," The San Diego Union, Sunday, 22 February 1981, p. H-15.
710. F. Honda, M. Kimura, S. Ozaki, K. Tamagori, T. Ohmi, H. Yoshikawa, "Flexible manufacturing system complex provided with laser — a national R & D program of Japan," Proc. IFAC Symposium on Information-Control Problems in Manufacturing Technology, September 1979, pp. 7-11.
711. Tihamer Toth-Fejel, "Modeling kinematic cellular automata: An approach to self-replication," Environmental Research Institute of Michigan, Ann Arbor, MI, 4 October 2000.
712. FANUC, "New Robot Factory started the full Operation," News Track, April 1998; http://www.fanuc.co.jp/en/news/h10/h10_04.htm.
713. Robot Factory, http://www.fanuc.co.jp/eannai/servo.htm; citation courtesy of Tihamer Toth-Fejel, 2000.
714. Tohru Watanabe, Watanabefv@aol.com, Department of Robotics, Ritsumeikan University; personal email communication to Tihamer Toth-Fejel, 21 March 2000.
715. Kathryn Stecke, University of Michigan, co-chair of the 2001 Symposium on Intelligent Automated Manufacturing (IAM'2001), personal email to Tihamer Toth-Fejel, Monday, 20 March 2000, 5:57 PM. See also John Heartly, "Mammoth FMS", The FMS Magazine (October 1983) and Raymond Chalmers, "Marrying CNC with the PC is the heart of the Cyber Factory", Manufacturing Engineering (September 1998).
716. FANUC Robot Products, 2003; http://www.fanuc.co.jp/en/product/m_robot.htm.
717. FANUC Factory Group, "Robot Factory," 2003; http://www.fanuc.co.jp/en/profile/production/factory2.htm.
718. Scott Bury, "Interconnectivity the key to wired future," Advanced Manufacturing; http://www.advancedmanufacturing.com/technologies.htm.
719. Don Golding, "Lights out factories," TIES Magazine, November/December 1995; http://www.angelusresearch.com/lightout.htm.
720. Carlye Adler, "Unifi: Tightening starts at home," Fortune, November 1999; http://www.business2.com/articles/mag/1,1640,5670,00.html.
721. J. Markoff, "All NeXT's Factory Lacks is Orders: Computers Operate Robot Assemblers," New York Times, Monday, 24 December 1990, p. 23.
722. Charles E. Taylor, "Fleshing out Artificial Life II," in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, SFI Studies in the Sciences of Complexity, Volume X, Addison-Wesley, Redwood City, CA, 1992, pp. 25-38.
723. Janine Krasicky, "Lights out system improves high-production machining process," FANUC Robotics North America Inc.; http://www.robotics.org/public/articles/index.cfm?cat=119; http://www.fanucrobotics.com/b/b1/b1i7_ct.html.
724. "Exhibition of Dream Technologies for the 21st Century," FANUC Ltd., July 2000; http://www.fanuc.co.jp/en/news/h1207/h1207_yumetech.htm.
725. "ROBOT CELL Enables 72-Hour Unmanned Operation," FANUC Ltd., June 2002; http://www.fanuc.co.jp/en/news/0206/0206_robotcell.html.
726. "Intelligent Robot System for Machining," FANUC Ltd., 4 March 2003; http://www.fanuc.co.jp/en/product/new_product/0210/robotsystem.html.
727. "New machining factory added to Hayato Factory: Shinto ritual," FANUC Ltd., May 2001; http://www.fanuc.co.jp/en/news/h1305/h1305_hayato.htm.
728. "Haas builds 608 machines in October," CNC Machining Magazine 5(Winter 2001); http://www.cncmagazine.com/v5i16/v5i16c-indnews.htm.
729. Alan E. Frisbie, "Tour of Fadal and Haas factories," 16 January 1996; http://yarchive.net/metal/cnc_tour.html.
730. Michael Page, "Make them at home," Production Machining (The Online Magazine of Screw Machine Technology); http://www.production-machining.com/columns/0701eur.html.
731. William Greider, "Chapter 6: Oversupply and Globalization of the Economy," One World, Ready or Not: The Manic Logic of Global Capitalism, Simon and Schuster, New York, 1997; http://jerome.net.free.fr/public/jnet/oversupply.htm.
732. Anant Kumar, Douglas Scott, Uri Kozai, "MES: Integratable systems in the semiconductor industry," Promis Systems Corp., Ltd., 1998; http://www.pria.com/products/fms/promis/pr_fms_promis_MES.pdf.
733. John W. Clemons, "The Manufacturing Execution System: facilitating people-integrated manufacturing," Industrial Computer Society, 1997; http://www.ics.org/memOnly/conference/papers/94_611.html.
734. Integrated Manufacturing Technology Initiative, "Section 5: Assembly," Manufacturing Processes & Equipment Roadmap, 24 July 2000; http://imti21.org/Documents/Roadmaps/MPE/MPChap5.pdf.
735. V.M.A. Chadeev, Self-Reproducing of Automata, Izdatel 'stvo Nauka, Moscow, 1973. In Russian.
736. V.M. Chadeev, "Allowance for robot self-replication in industrial automation," Automation and Remote Control 61(October 2000):1752-1757; http://www.maik.rssi.ru/abstract/autorcb/0/autorcb1752_abstract.pdf (abstract).
737. Yoshiaki Ichikawa, "Communication and control for self-reproducing robots," J. Robotics Soc. Japan 12(September 1994):13-17 (Special Issue: Network Type Robot System); http://www.sanbi.co.jp/rsj/PDF/Vol_12/No_06/1206B013.pdf.
738. Robert A. Frosch, Nicholas E. Gallopoulos, "Strategies for manufacturing," Sci. Am. 261(September 1989):94-102.
739. Peter Baccini, Paul Brunner, Metabolism of the Anthroposphere, Springer-Verlag, Berlin, 1991.
740. Robert A. Frosch, Nicholas E. Gallopoulos, "Towards an industrial ecology," in A.D. Bradshow et al, eds., The Treatment and Handling of Wastes, Chapman & Hall, London, 1992, pp. 269-292.
741. Robert U. Ayres, Udo E. Simonis, eds., Industrial Metabolism. Restructuring for Sustainable Development, United Nations University Press, New York, 1994.
742. Robert U. Ayres, Leslie W. Ayres: Industrial Ecology. Towards Closing the Materials Cycle, Edward Elgar, Cheltenham, UK, 1996.
743. Suren Erkman, "Industrial ecology: An historical view," J. Cleaner Production 5(1997):1-10. See also the extended and revised paper: Suren Erkman, "The recent history of industrial ecology," in Robert U. Ayres, Leslie W. Ayres, eds., A Handbook of Industrial Ecology, Edward Elgar, Cheltenham, UK, 2002, pp. 27-35.
744. Braden R. Allenby, "Earth systems engineering: The role of industrial ecology in an engineered world," J. Industrial Ecology 2(1998):73-93.
745. Suren Erkman, "Industrial ecology: a new perspective on the future of the industrial system," Swiss Medical Weekly 131(2001):531-538. Earlier version previously published as: Suren Erkman, "Industrial Ecology: a new perspective on the future of the industrial system," President's lecture, Assemblée annuelle de la Société Suisse de Pneumologie, Genève, 30 March 2001; http://www.chairetmetal.com/cm06/erkman-complet.htm.

746. S. Kalpakjian, Manufacturing Engineering and Technology, Addison-Wesley Publishing Company, New York, 1995.
747. Farid M.L. Amirouche, Computer-Aided Design and Manufacturing, Prentice-Hall, NJ, 1992.
748. Hans B. Kief, T. Frederick Waters, Computer Numerical Control, Glencoe McGraw Hill, 1992.
749. Tien-Chien Chang, Richard A. Wysk, Hsu-Pin Wang, Computer-Aided Manufacturing, Second Edition, Prentice Hall, NJ, 1997.
750. A. Delchambre, ed., CAD Method for Industrial Assembly: Concurrent Design of Products, Equipment and Control Systems, John Wiley & Sons, New York, 1997.
751. Kunwoo Lee, Principles of CAD/CAM/CAE Systems, Addison-Wesley Publishing Co., New York, 1999.
752. "Welcome to eMachineShop — where you can design, price, and order your custom parts online," 2004; http://www.emachineshop.com.
753. A. Adlemo, S.-A. Andreasson, "A dependability taxonomy for intelligent manufacturing systems," Intl. J. Comp. Integ. Manuf. 8(1995):189-196.
754. IFAC Workshop, Intelligent Manufacturing Systems 1997, Pergamon Press, New York, 1998.
755. P. Kopacek, C.E. Pereira, eds., Intelligent Manufacturing Systems 1998, Pergamon Press, New York, 2000.
756. Edward A. Rietman, Ralph E. Taylor Smith, Intelligent Manufacturing, Computerized Factories, CRC Press, 2001.
757. P. Kopacek, ed., Intelligent Assembly and Disassembly, IAD'98, Pergamon Press, 1998.
758. Tadeusz Sawik, Production Planning and Scheduling in Flexible Assembly Systems, Springer-Verlag, 1999.
759. R. Simmons, S. Singh, D. Hershberger, J. Ramos, T. Smith, "Coordination of heterogeneous robots for large-scale assembly," in Proc. 7th Intl. Symposium on Experimental Robotics (ISER), Springer-Verlag, Berlin, 2000; http://www.contrib.andrew.cmu.edu/~trey/academic/papers/simmons00_coordination.pdf.
760. Nand K. Jha, Handbook of Flexible Manufacturing Systems, Academic Press, New York, 1991.
761. Ronald G. Askin, Charles Standridge, Modeling and Analysis of Manufacturing Systems, John Wiley & Sons, New York, 1993.
762. Horst Tempelmeier, Heinrich Kuhn, Flexible Manufacturing Systems: Decision Support for Design and Operation, John Wiley & Sons, New York, 1993.
763. Lee R. Nyman, ed., Making Manufacturing Cells Work, McGraw-Hill, New York, 1994.
764. A. Adlemo, S.-A. Andreasson, M. Fabian, P. Gullander, B. Lennartsson, "Towards a truly flexible manufacturing system," Control Engineering Practice 3(April 1995):545-554.
765. Ali K. Kamrani, Hamid R. Parsaei, Donald H. Liles, eds., Planning, Design, and Analysis of Cellular Manufacturing Systems, Elsevier Science Ltd., 1995.
766. A. Adlemo, S.-A. Andreasson, "Balanced automation in flexible manufacturing systems," Intl. J. Studies Informatics and Control 5(June 1996):179-187.
767. Daniel Sipper, Robert Bulfin, Production: Planning, Control and Integration, McGraw-Hill, New York, 1997.
768. M. Fabian, B. Lennartsson, P. Gullander, S.-A. Andreasson, A. Adlemo, "Chalmers architecture and methodology for flexible production — CHAMP," in N. Martensson et al, eds., Changing the Ways We Work, IOS Press, 1998, pp. 720-731.
769. Steven A. Melnyk, Ram Narasimhan, Computer Integrated Manufacturing: Guidelines and Applications from Industrial Leaders, McGraw-Hill Publ. Co., New York, 1991.
770. Arthur L. Foston, Carolena L. Smith, Tony Au, Fundamentals of Computer Integrated Manufacturing, Prentice-Hall, NJ, 1997.
771. Russell Biekert, David Berling, Richard J. Evans, Donald G. Kelley, CIM Technology: Fundamentals and Applications, Goodheart-Willcox, 1998.
772. Roger Hannam, Computer Integrated Manufacturing: From Concepts to Realization, Addison-Wesley Publ. Co., New York, 1998.
773. S. Kant Vajpayee, Principles of Computer Integrated Manufacturing, Prentice Hall, NJ, 1998.
774. James A. Rehg, Introduction to Robotics in CIM Systems, Prentice Hall, NJ, 1999.
775. A. Sen, A.I. Sivakuma, R. Gay, eds., Computer Integrated Manufacturing, Proc. Fourth Intl. Conf., 21-24 October 1997, Singapore, Springer-Verlag, NY, 1999.
776. Mikell P. Groover, Automation, Production Systems, and Computer-Integrated Manufacturing, Prentice Hall, NJ, 2000.
777. James A. Rehg, Henry W. Kraebber, Computer-Integrated Manufacturing, Prentice Hall, NJ, 2000.
778. Cornelius Leondes, ed., Computer Integrated Manufacturing, CRC Press, 2001.
779. Tarun Gupta, Computer-Integrated Manufacturing and Mechatronics, CRC Press, 2002.
780. M.S. Miller, K.E. Drexler, "Markets and computation: agoric open systems," in Bernardo A. Huberman, ed., The Ecology of Computation, Elsevier Science Publ., Amsterdam, 1988, http://www.agorics.com/Library/agoricpapers/aos/aos.0.html; K.E. Drexler, M.S. Miller, "Incentive engineering for computational resource management," in Bernardo A. Huberman, ed., The Ecology of Computation, Elsevier Science Publ., Amsterdam, 1988, http://www.agorics.com/Library/agoricpapers/ie/ie0.html; M.S. Miller, K.E. Drexler, "Comparative ecology: a computational perspective," in Bernardo A. Huberman, ed., The Ecology of Computation, Elsevier Science Publ., Amsterdam, 1988, http://www.agorics.com/Library/agoricpapers/ce/ce0.html.
781. Oliver Guenther, Tad Hogg, Bernardo A. Huberman, "Market organizations for controlling smart matter," in R. Conte, R. Hegselmann, P. Terna, eds., Simulating Social Phenomena, Lecture Notes in Economics and Mathematical Systems, Springer, 1997, pp. 241-257; Oliver Guenther, Tad Hogg, Bernardo A. Huberman, "Power markets for controlling smart matter," arXiv:cond-mat/9703078 v1 7 March 1997, 20 December 2001; http://arxiv.org/pdf/cond-mat/9703078. See also: Tad Hogg, Bernardo A. Huberman, "Controlling Smart Matter," Smart Materials and Structures 7(1998):R1-R14; http://www.arxiv.org/abs/cond-mat/9611024.
782. J. Storrs Hall, Louis Steinberg, Brian D. Davison, "Combining agoric and genetic methods in stochastic design," Nanotechnology 9(September 1998):274-284; http://www.cs.rutgers.edu/~davison/pubs/chsmith/chsmith.html.
783. Tihamer Toth-Fejel, "Agents, assemblers, and ANTS: scheduling assembly with market and biological software mechanisms," Nanotechnology 11(June 2000):133-137; http://www.erim.org/cec/papers/NanoAgents.pdf.
784. Stepas Janusonis, "Self-formation technology," Informatica 2(October-December 1991):497-515; http://www.mii.lt/mii_inform/volume2.htm#v243 (abstract).
785. Stepas Janusonis, "Self-formation in microelectronics," AI EDAM 14(June 2000):221-234.
786. Stepas Janusonis, Vida Janusoniene, Self-Formation of Artificial Systems. Theory and Application, Institute of Lithuanian Scientific Society, Vilnius, Lithuania, 2001; http://msi.lms.lt/rtdresult/self_e.html.
787. FirstStep (Self-Formation Research Towards Stairway to Excellence in Photovoltaic), Institute of Lithuanian Scientific Society, 2003; http://firststep.self-formation.lt/index.html.
788. 6th International Conference and Exhibition, Self-Formation Theory and Application, 26-28 November 2003, Vilnius, Lithuania; http://www.self-formation.lt/.
789. D.M. Dilts, N.P. Boyd, H.H. Whorms, "The evolution of control architectures for automated manufacturing systems," J. Manufacturing Systems 10(January 1991):79-93.
790. SciNet, "Production mini-plants in mobile containers," SciNet Corp., 2002; http://www.scinet-corp.com/associates/index.htm?miniplants.htm~index2.
791. SciNet, "Assembly plants," SciNet Corp., 2002; http://www.scinet-corp.com/associates/assembly_plant.htm.
792. SciNet, "Assembly Plant for the manufacture in series of production Mini-plants," SciNet Corp., 2002; http://www.ist-sci.com/miniplants/sc/sc_production_miniplants_eng.pdf.
793. Kenneth Chang, "Can robots rule the world? Not yet," The New York Times, 12 September 2000; http://www.nytimes.com/2000/09/12/science/12ROBO.html?ex=1049259600&en=1ffbff5f30988a75&ei=5070.
794. Hans Moravec, Robot: Mere Machine to Transcendent Mind, Oxford University Press, 1999.
795. Raj Reddy, "Technologies for the Future — Speakers Profile," Conferences@Bangalore IT.COM 2000; http://www.bangaloreit.com/html/itscbng/technospeak.htm.
796. Raj Reddy, Simon University Professor, RI/CS, Carnegie Mellon University, Robotics Institute, "Research Interests," April 2003; http://www.ri.cmu.edu/people/reddy_raj.html.

797. Armin Hemmerling, “Systeme von Turing-Automaten und Zellularräume auf rahmbaren Pseudomustermengen,” Elektronische Informationsverarbeitung und Kybernetik, 15(1979):47-72. In German.
798. Armin Hemmerling, “Concentration of multidimensional tape-bounded systems of Turing automata and cellular spaces,” in L. Budach, ed., Fundamentals of Computation Theory, Akademie-Verlag, Berlin, 1979, pp. 167-174.
799. Richard L. Thompson, Narendra S. Goel, “Movable finite automata (MFA) models for biological systems. I. Bacteriophage assembly and operation,” J. Theor. Biol. 131(7 April 1988):351-385.
800. Narendra S. Goel, Richard L. Thompson, “Movable finite automata (MFA) models for biological systems. II. Protein biosynthesis,” J. Theor. Biol. 134(9 September 1988):9-49.
801. Narendra S. Goel, Richard L. Thompson, Computer Simulation of Self-organization in Biological Systems, Macmillan, New York, 1988.
802. Narendra S. Goel, Richard L. Thompson, “Movable finite automata (MFA): A new tool for computer modeling of living systems,” in Christopher G. Langton, ed., Artificial Life, Studies in the Sciences of Complexity, Santa Fe Institute, Volume VI, Addison-Wesley, New York, 1989, pp. 317-340.
803. Marek W. Lugowski, “Computational metabolism: Towards biological geometries for computing,” in Christopher G. Langton, ed., Artificial Life, Studies in the Sciences of Complexity, Santa Fe Institute, Volume VI, Addison-Wesley, New York, 1989, pp. 341-368.
804. S.G. Psakhie, Y. Horie, S.Yu. Korostelev, A.Yu. Smolin, A.I. Dmitriev, E.V. Shilko, S.V. Alekseev, “Method of movable cellular automata as a tool for simulation within the framework of mesomechanics,” Russian Physics Journal 38(November 1995):1157-1168.
805. S.G. Psakhie, S.Yu. Korostelev, A.Yu. Smolin, A.I. Dmitriev, E.V. Shilko, D.D. Moiseyenko, E.M. Tatarintsev, S.V. Aleksov, “Movable cellular automata method as a tool for physical mesomechanics of materials,” Physical Mesomechanics 1(1998):89-101; http://www.ispms.tsc.ru/eng/PhysMesomech/1998/num1/p089101e.html.
806. S.G. Psakhie, D.D. Moiseyenko, A.Yu. Smolin, E.V. Shilko, A.I. Dmitriev, “A study of fracture peculiarities of brittle ceramic coatings by the movable cellular automata method,” Physical Mesomechanics 2(1998):89-94; http://www.ispms.tsc.ru/eng/PhysMesomech/1998/num2/p089094e.html; see also: Aleksei Smolin, http://pampero.ijs.si/vitae.html.
807. Andrew Adamatzky, Computing in Nonlinear Media and Automata Collectives, Institute of Physics Publishing, 2001.
808. Andrew Adamatzky, Owen Holland, “Phenomenology of excitation in 2-D cellular automata and swarm systems,” No. S134, Fourth European Conference on Artificial Life (ECAL’97), in Chaos, Solitons and Fractals (1998):1233-1265; see: http://citeseer.nj.nec.com/update/16715 (abstract) and ftp://ftp.cogs.susx.ac.uk/pub/ecal97/online/F134.ps.gz (paper).
809. P. Lerena, M. Courant, “Bio-machines,” poster presentation in Proceedings of Artificial Life V, Nara, Japan, 1996.
810. Kohji Tomita, Haruhisa Kurokawa, Satoshi Murata, “Graph automata: natural expression of self-reproduction,” Physica D 171(2002):197-210.
811. Catie Chang, “Self-assembling two-dimensional shapes,” UROP, Summer 2002; http://swiss.csail.mit.edu/projects/amorphous/Robust/catie/.
812. Rebecca Bloom, Catherine Chang, Attila Kondacs, “Compilation and biologically-inspired self-assembly of two-dimensional shapes,” Final Project Paper, Biologically Motivated Programming Technology for Robust Systems, MIT Course 6.978, December 2002; http://www.swiss.ai.mit.edu/projects/amorphous/6.978/final-papers/attila-catie-rebecca-final.pdf.
813. Attila Kondacs, “Biologically-inspired self-assembly of 2-D shapes, using global-to-local compilation,” Intl. Joint Conf. on Artif. Intell. (IJCAI’03), 2003; http://www.swiss.ai.mit.edu/projects/amorphous/papers/IJCAI-03.pdf.
814. Radhika Nagpal, Attila Kondacs, Catherine Chang, “Programming methodology for biologically-inspired self-assembling systems,” AAAI Spring Symposium on Computational Synthesis: From Basic Building Blocks to High Level Functionality, March 2003; http://www.swiss.ai.mit.edu/projects/amorphous/papers/aaai-symp03.pdf.
815. Tihamer Toth-Fejel, “LEGOs^{TM} to the stars: Active mesostructures, kinematic cellular automata, and parallel nanomachines for space applications,” The Assembler 4(Third Quarter 1996):2-12; http://www.islandone.org/MMSG/9609lego.htm.
816. Joseph Michael, “Programmable materials,” United States Patent No. 6,157,872, 5 December 2000; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,157,872.WKU.&OS=PN/6,157,872; Foreign Application Priority Data: U.K. 9404227, 4 March 1994.Invention originally patented in U.K. as: Joseph Michael, “Programmable materials,” Great Britain Patent No. GB19940004227, 8 September 1995. U.K. patent originally filed 3 March 1995; http://l2.espacenet.com/espacenet/viewer?PN=GB2287045&CY=gb&LG=en&DB=EPD.
817. S. Kokaji, “A Fractal Mechanism and a Decentralized Control Method,” Proc. US-Japan Symp. Flexible Automation Minneapolis, 1988.7.
818. J.S. Hall, “Utility Fog: A Universal Physical Substance,” Vision-21: Interdisciplinary Science and Engineering in the Era of Cyberspace, Westlake, OH; NASA Conference Publication CP-10129, 1993, pp. 115-126; http://www.aeiveos.com/~bradbury/Authors/Computing/Hall-JS/UFAUPS.html.
819. J. Storrs Hall, “Utility Fog, Part I,” Extropy 6(QIII, 1994):16-20; “Utility Fog, Part II,” Extropy 7(QI, 1995):7-12; http://nanotech.rutgers.edu/nanotech/Ufog.html and http://nanotech.rutgers.edu/nanotech/papers/utility.fog.
820. J. Storrs Hall, “Utility Fog: The stuff that dreams are made of,” in B.C. Crandall, ed., Nanotechnology: Molecular Speculations on Global Abundance, MIT Press, Cambridge, MA, 1996, pp. 161-184; http://www.kurzweilai.net/meme/frame.html?main=/articles/art0220.html?m%3D7.
821. S. Murata, H. Kurokawa, S. Kokaji, “Self-assembling machine,” Proc. 1994 IEEE Intl. Conf. On Robotics and Automation, San Diego, CA, 1994, pp. 441-448.
822. E. Yoshida, S. Murata, K. Tomita, H. Kurokawa, S. Kokaji, “An experimental study on a self-repairing modular machine,” Robotics and Autonomous Systems 29(1999):79-89.
823. K. Tomita, S. Murata, H. Kurokawa, E. Yoshida, S. Kokaji, “A Self-Assembly and Self-Repair Method for a Distributed Mechanical System,” IEEE Transactions on Robotics and Automation, 15(1999):1035-1045.
824. Joseph Michael, “Shape Changing Robots,” Electronics Today International (December 1995):10-17; “Robocube — British inventor Joe Michael defines the shape of industrial robots to come,” Esquire (March 1996):156; “Fractal Robots,” Smart Materials & Systems (February 1997):56-65; “The Shape of Robots to Come?” Business Week Euro. Edition (1 February 1999):62-64.
825. Forrest Bishop, “The construction and utilization of space filling polyhedra for active mesostructures,” Institute for Atomic Scale Engineering, 7 December 1995; http://www.iase.cc/html/active_cells.htm.
826. Forrest Bishop, “The shape of things to come: Shape-shifting matter, self-replicating interstellar nNanoprobes, Drexler universal assemblers…,” NanoTechnology Magazine 2(April 1996):4-7; http://www.iase.cc/html/future.htm.
827. Forrest Bishop, “A proposed MNT active cell,” Institute for Atomic Scale Engineering, 1996; http://www.iase.cc/html/mntcell.htm.
828. Forrest F. Bishop, “A description of a universal assembler,” Proc. IEEE Intl. Joint Symposia on Intelligence and Systems, 4-5 November 1996, Rockville, MD, USA (ISBN 0-8186-7728-7), 1996; http://www.iase.cc/html/universal.htm. See also: Forrest Bishop, “The overtool: A proposed universal assembler,” Institute for Atomic Scale Engineering, 1996; http://www.iase.cc/html/overtool.htm.
829. Mark Thorson, “”Kram: The Universal Material,” unpublished manuscript, 1991; cited in Tom McKendree, “The logical core architecture,” Nanotechnology 9(September 1998):212-222; http://www.foresight.org/Conferences/MNT05/Papers/McKendree/index.html.
830. Mark Yim, John Lamping, Eric Mao, J. Geoffrey Chase, “Rhombic dodecahedron shape for self-assembling robots,” DARPA Contract #DABT630095C-025, Xerox PARC SPL TechReport P97-10777, 1997; http://www.parc.xerox.com/spl/projects/modrobots/Publications/rdtechreport.pdf or http://www2.parc.com/spl/WWW/modrobots/Publications/rdtechreport.pdf. See also: M. Yim, Y. Zhang, J. Lamping, E. Mao, “Distributed control for 3-D metamorphosis,” Autonomous Robots 10(2001):41-56.
831. I.-M. Chen, J.W. Burdick, “Enumerating non-isomorphic assembly configurations of a modular robotic system,” IEEE/RSJ International Conference on Intelligent Robots and Systems, Yokohama, Japan, 1993, pp. 1985-1992.

832. I.-Ming Chen, Theory and Applications of Modular Reconfigurable Robotic Systems, Ph.D. Thesis, Division of Engineering and Applied Science, California Institute of Technology, 1994.

833. I.-M. Chen, J.W. Burdick, "Determining task optimal modular reconfigurable robot assembly configurations," IEEE International Conference on Robotics and Automation, Japan, 1995, pp. 132-137.

834. Thomas Alva Edison as quoted by George Lathrop, Harper's Magazine, Issue 80, 1890; reported in: Paul Israel, Edison: A Life of Invention, John Wiley & Sons, New York, 1998.

835. Richard R. Landers, Man's Place in the Dybosphere, Prentice-Hall, Englewood Cliffs, NJ, 1966.

836. T. Erber, G.R. Marousek, G.K. Forsberg, "Study of a magnetic cooperative system," Acta Physica Austriaca 30(1969):271-294.

837. Michio Okuma, Isao Todo, "Assembly method of blocks for structures," Trans. Jpn. Soc. Mech. Eng. 59C(March 1993):791-798. In Japanese.

838. Michio Okuma, Isao Todo, "Application of systematic mechanisms in living beings to robot systems design," Proc. 1993 IEEE/RSJ Intl. Conf. On Intelligent Robots and Systems (IROS'93), Yokohama, Japan, 26-30 July 1993, Volume I, pp. 209-216.

839. Larry Yaeger, "T2 and Technology," http://www.beanblossom.in.us/larryy/T2Tech.html.

840. "Terminator 2: Judgment Day," directed by James Cameron, a Pacific Western production in association with Lightstorm Entertainment, 1991; http://www.movieprop.com/tvandmovie/terminator/T2.htm, http://www.filmsite.org/term2.html.

841. T. Fukuda, S. Nakagawa, "Dynamically reconfigurable robotic systems," Proc. IECON'87, 1987, pp. 588-595; Proc. IEEE Intl. Conf. Robotics and Automation, 1988, pp. 1581-1586.

842. T. Fukuda, S. Nakagawa, Y. Kawauchi, M. Buss, "Self organizing robots based on cell structures — CEBOT," Proc. IEEE Intl. Workshop on Intelligent Robots and Systems (IROS'88), Science Univ. of Tokyo, 1988, pp. 145-150.

843. Toshio Fukuda, Yoshio Kawauchi, "Cellular robotic system (CEBOT) as one of the realization of self-organizing intelligent universal manipulator," Proc. 1990 IEEE Intl. Conf. On Robotics and Automation, 13-18 May 1990, Cincinnati, OH, IEEE Computer Society Press, Washington DC., 1990, pp. 662-667.

844. T. Fukuda, S. Nakagawa, F. Hara, "Dynamic distributed knowledge system in self-organizing robotic systems: CEBOT," Proc. IEEE Intl. Conf. Robotics and Automation, 1991, pp. 1908-1913.

845. T. Fukuda, T. Ueyama, F. Arai, "Control strategies for cellular robotic network," in A.H. Lewis, H.E. Stephanou, eds., Distributed Intelligence Systems, Pergamon Press, Oxford, 1992, pp. 177-182.

846. Toshio Fukuda, Yoshio Kawauchi, "Cellular robotics: construction of complicated systems from simple functions," in Paolo Dario, Giulio Sandini, Patrick Aebischer, eds., Robots and Biological Systems: Towards a New Bionics? Springer-Verlag, New York, 1993, pp. 745-782.

847. Toshio Fukuda, Kousuke Sekiyama, Tsuyoshi Ueyama, Fumihito Arai, "Efficient communication method in the cellular robotic system," in Proc. 1993 IEEE/RSJ Intl. Conf. On Intelligent Robots and Systems (IROS'93), Yokohama, Japan, 26-30 July 1993, Volume II, pp. 1091-1096.

848. Department of Mechano-Informatics System Engineering, Center for Cooperative Research in Advanced Science and Technology, Nagoya University, Japan; http://www.mein.nagoya-u.ac.jp/activity/introduction.html#CEBOT.

849. T. Fukuda, T. Ueyama, Cellular Robotics and Micro Robotic Systems, World Scientific Publishing Co., Singapore, 1994.

850. N. Mitsumoto, T. Fukuda, K. Shimojina, A. Ogawa, "Micro autonomous robotic system and biologically inspired immune system swarm strategy as a multi agent robotic system," Proc. IEEE Intl. Conf. On Robotics and Automation, 1995, pp. 2187-2192; Toshio Fukuda, Hiroo Mizoguchi, Fumihito Arai, Kosuke Sekiyama, "Micro Autonomous Robot Systems (MARS): Coordination and control of multiple micro robots," J. Micromechatronics 1(July 2001):239-251.

851. Mark Yim, "Locomotion with a unit-modular reconfigurable robot," Stanford University Technical Report STAN-CS-TR-95-1536; http://robotics.stanford.edu/users/mark/polypod.html.

852. Mark Yim, David G. Duff, Kimon D. Roufas, "PolyBot: a modular reconfigurable robot," IEEE Intl. Conf. on Robotics and Automation (ICRA) 2000, http://www.parc.xerox.com/spl/projects/modrobots/Publications/publications.htm; see also "Polybot" at: http://www.parc.xerox.com/spl/projects/modrobots/PolyBot/polybot.htm; photos from: http://www.parc.xerox.com/spl/projects/modrobots/PolyBot/demos.htm.

853. M. Yim, Y. Zhang, D. Duff, "Modular robots," IEEE Spectrum 39(2002):30-34.

854. M. Yim, "A reconfigurable modular robot with many modes of locomotion," Proc. 1993 JSME Intl. Conf. on Advanced Mechatronics, Tokyo, Japan, August 1993, pp. 283-288.

855. Mark Yim, "Morphing Robots," March 1998; http://www.parc.xerox.com/spl/projects/modrobots/RD/RD.html.

856. Tad Hogg, personal communication to Robert A. Freitas Jr., 9 September 2003.

857. Hristo Bojinov, Arancha Casal, Tad Hogg, "Multiagent Control of Modular Self-Reconfigurable Robots," Artificial Intelligence 142(2002):99-120; http://www.arxiv.org/cs.RO/0006030.

858. Jeremy Kubica, Arancha Casal, Tad Hogg, "Agent-based control for object manipulation with modular self-reconfigurable robots," Proc. 17th Intl. Joint Conf. on Artificial Intelligence (IJCAI-2001), Morgan Kaufmann, San Francisco, 2001, pp. 1344-1349.

859. J. Kubica, A. Casal, T. Hogg, "Complex behaviors from local rules in modular self-reconfigurable robots," IEEE Intl. Conf. on Robotics and Automation (ICRA), Seoul, Korea, May 2001; http://www2.parc.com/spl/projects/modrobots/publications/research/index.html#icra01telecube.

860. J. Suh, S. Homans, M. Yim, "Design tradeoffs for modular self-reconfigurable robots: the mechanical design of telecubes (a case study in progress)," IEEE Intl. Conf. on Robotics and Automation (ICRA) Workshop on Self-reconfigurable Robots, Seoul, Korea, May 2001; http://www2.parc.com/spl/projects/modrobots/publications/research/index.html#icra01ws.

861. Xerox PARC, "Modular Robotics Telecube: A Self-assembling Lattice Reconfiguration Robot," January 2002; http://www.parc.xerox.com/spl/projects/modrobots/lattice/telecube/.

862. S. Vassilvitskii, J. Suh, M. Yim, "A complete, local and parallel reconfiguration algorithm for cube style modular robots," accepted to 2002 IEEE Intl. Conf. on Robotics and Automation (ICRA); http://www2.parc.com/spl/projects/modrobots/publications/research/index.html#icra02planning.

863. S. Vassilvitskii, J. Kubica, E. Rieffel, J. Suh, M. Yim, "On the general reconfiguration problem for expanding cube style modular robots," accepted to 2002 IEEE Intl. Conf. on Robotics and Automation (ICRA); http://www2.parc.com/spl/projects/modrobots/publications/research/index.html#icra02reconfig.

864. J. Suh, S. Homans, M. Yim, "Telecubes: Mechanical design of a module for self-reconfigurable robotics," submitted to 2002 IEEE Intl. Conf. on Robotics and Automation (ICRA); http://www2.parc.com/spl/projects/modrobots/publications/research/index.html#icra02telecube.

865. Xerox PARC, "Modular Robotics Telecube: Demonstrations and simulation. Videos of prototype functionality," January 2002; http://www.parc.xerox.com/spl/projects/modrobots/lattice/telecube/.

866. A. Castano, W.-M. Shen, P. Will, "CONRO: Towards deployable robots with inter-robot metamorphic capabilities," Autonomous Robots 8(2000):309-324. See also the USC/ISI CONRO Project; http://www.isi.edu/conro/ . See also: Michael Rubenstein, Kenneth Payne, Peter Will, Wei-Min Shen, "Docking Among Independent and Autonomous CONRO Self-Reconfigurable Robots," Information Sciences Institute (ISI), USC, 2003; http://www.isi.edu/robots/papers/221.pdf; "Space Assembly and Service via Self-Reconfiguration," http://www.isi.edu/robots/solar/intro.pdf; "Self-Assembly in Space via Self-Reconfigurable Robots," http://www.isi.edu/robots/papers/icra03 ssps final.pdf; Philip Ball, "Puckish robots pull together," Nature Science Update, 28 May 2004; http://www.nature.com/nsu/040524/040524-9.html; "Robotic Space Workers of the Future," Roland Piquepaille's Technology Trends, 29 May 2004; http://radio.weblogs.com/0105910/2004/05/29.html.

867. D. Rus, G. Chirikjian, eds., Special Issue on Self-Reconfiguring Robots, Autonomous Robots 10(January 2001):1-124.

868. Johns Hopkins University, Robot Kinematics and Motion Planning Lab; http://robotics.jhu.edu/.

869. Joseph Michael, "Current electrically operated prototypes," Digital Matter Control Web Site, 2001; http://www.stellar.demon.co.uk/developers.htm; "MEMS," Digital Matter Control Web Site, 2001; http://www.stellar.demon.co.uk/mems.htm.
870. Eiichi Yoshida, "Distributed self-reconfiguration of 3-D homogenous modular structure," Mechanical Engineering Laboratory (MEL), Agency of Industrial Science and Technology, Ministry of International Trade and Industry, Japan, 2001; http://www.mel.go.jp/soshiki/buturi/system/yoshida/3dunit/3dunit-e.htm. See also: "Two Dimensional Self-Assembling/Self-Repairing Machine; http://www.mel.go.jp/soshiki/buturi/system/murata/fractum-e.htm.
871. "The Crystalline Robot," Dartmouth Robotics Lab; http://www.cs.dartmouth.edu/~robotlab/robotlab/robots/crystal/ or http://www.ai.mit.edu/~vona/xtal/.
872. Daniela Rus, Zack Butler, Keith Kotay, Marsette Vona, "Self-reconfiguring robots," Commun. ACM 45(March 2002):39-45; http://www.ai.mit.edu/~vona/publications/cacm02.pdf.
873. Zack Butler, Daniela Rus, "Self-replicating robots for monitoring and surveillance," Dartmouth University poster presentation at the Workshop on Intelligent Human Augmentation and Virtual Environments (WIHAVE), 17-19 October 2002; http://www.cs.unc.edu/~geom/WIHAVE/POSTERS/FINAL/rusbutler.pdf.
874. Zack Butler, Satoshi Murata, Daniela Rus, "Distributed replication algorithms for self-reconfiguring modular robots," Dartmouth College Robotics Lab, to appear in DARS2002; http://www.cs.dartmouth.edu/~robotlab/robotlab/papers/zackb/dars02.pdf.
875. K. Kotay, D. Rus, M. Vona, C. McGray, "The self-reconfiguring molecule: design and control algorithms," in P. Agrawal, L. Kavraki, M. Mason, eds., Algorithmic Foundations of Robotics, A.K. Peters, 1998; http://www.cs.dartmouth.edu/~robotlab/robotlab/papers/1.ps.Z; C. McGray, D. Rus, "Self-reconfiguring molecules as 3-D metamorphic robots," in Proc. 1998 Conference on Intelligent Robot Systems, 1998; http://www.cs.dartmouth.edu/~robotlab/robotlab/papers/5.ps.gz.
876. "The Molecule Robot," Dartmouth Robotics Lab; http://www.cs.dartmouth.edu/~robotlab/robotlab/robots/molecule/index.html.
877. M.T. Mason, D.K. Pai, D. Rus, J. Howell, L.R. Taylor, M.A. Erdmann, "Experiments with desktop mobile manipulators," Experimental Robotics VI Lecture Notes in Control and Information Science 250(2000):37-46.
878. Self-Reconfiguring Robots at the Dartmouth Robotics Lab; http://www.cs.dartmouth.edu/~rus/self-reconfig.html.
879. "MinDART — Minnesota Distributed Autonomous Robotics Team," Department of Computer Science and Engineering, University of Minnesota, September 2001; http://www.cs.umn.edu/Research/airvl/minirob/mindart/. See also University of Minnesota Center for Distributed Robotics; http://www.cs.umn.edu/research/airvl/distributed/index.html.
880. A.B. Neville, A.C. Sanderson, "TETROBOT: A Modular System for Hyperredundant Robotics," Proceedings of 1995 IEEE International Conference on Robotics and Automation, Nagoya, Japan, May 1995.
881. A.B. Neville, A.C. Sanderson, "Tetrobot family tree: modular synthesis of kinematic structures for parallel robotics," IEEE/RSJ Intl. Conf. on Intelligent Robots and Systems, November 1996, pp. 382-389.
882. G.J. Hamlin, A.C. Sanderson, Tetrobot: A Modular Approach to Reconfigurable Parallel Robotics, Kluwer Academic Publishers, Newton, MA, 1998; see Tetrobot website at: http://www.rpi.edu/~leew9/Tetrobot/tetrobot.html.
883. Woo Ho Lee, Arthur C. Sanderson, "Dynamic rolling, locomotion planning, and control of an icosahedral modular robot," IEEE/RSJ Intl. Conf. on Intelligent Robots and Systems, 31 October - 5 November 2000, Japan, pp. 2178-2183; http://www.rpi.edu/~leew9/Tetrobot/tet_design.html.
884. W.H. Lee, A.C. Sanderson, "Dynamic Analysis and Distributed Control of the Tetrobot Modular Reconfigurable Robotic System," Autonomous Robots 10(2001):67-82. (Special Issue on Reconfigurable Robotics).
885. Pradeep K. Khosla, Takeo Kanade, Christiaan J.J. Paredis, "Reconfigurable modular manipulator system," Advanced Mechatronics Laboratory, Carnegie Mellon University, Pittsburgh, PA, 2001; http://www-2.cs.cmu.edu/~paredis/rmms/.
886. Michigan State University College of Engineering, DARP Microrobot Project; http://www.egr.msu.edu/microrobot/.
887. "Modular robot ready to walk," Distributed System Design Group, Intelligent Systems Institute, AIST, Japan, July 2001; http://staff.aist.go.jp/e.yoshida/test/top-e.htm. See also: "Experiment of self-reconfiguration by 9-module," 2001; http://staff.aist.go.jp/e.yoshida/test/research-2-e.htm; and "M-TRAN II: Self-Reconfigurable Modular Robot," updated 18 November 2003; http://unit.aist.go.jp/is/dsysd/mtran/English/index.html.
888. S. Murata, E. Yoshida, A. Kamimura, H. Kurokawa, K. Tomita, S. Kokaji, "M-TRAN: Self-Reconfigurable Modular Robotic System," IEEE/ASME Trans. Mechatronics, 7(2002):431-441; see also http://unit.aist.go.jp/is/dsysd/mtran/English/index.html.
889. Eiichi Yoshida, Satoshi Murata, Akiya Kamimura, Kohji Tomita, Haruhisa Kurokawa, Shigeru Kokaji, "A Self-Reconfigurable Modular Robot : Reconfiguration Planning and Experiments," Intl. J. Robotics Res. 21(October 2002):903-916.
890. Eiichi Yoshida, Shigeru Kokaji, Satoshi Murata, Kohji Tomita, Haruhisa Kurokawa, "Miniaturization of Self-reconfigurable Robotic System using Shape Memory Alloy Actuator," J. Robotics and Mechatronics 12(2000):96-102.
891. Eiichi Yoshida, Shigeru Kokaji, Satoshi Murata, Kohji Tomita, Haruhisa Kurokawa, "Micro Self-reconfigurable Robot using Shape Memory Alloy," J. Robotics and Mechatronics 13(2001):212-219; http://staff.aist.go.jp/e.yoshida/smaunit/papers/rm00.pdf.
892. Eiichi Yoshida, Satoshi Murata, Akiya Kamimura, Shigeru Kokaji, Kohji Tomita, Haruhisa Kurokawa, "Get Back In Shape! A Hardware Prototype Self-Reconfigurable Modular Microrobot that Uses Shape Memory Alloy," IEEE Robotics & Automation Magazine 9(April 2002):54-60; http://staff.aist.go.jp/e.yoshida/smaunit/papers/ra-mag2002dec.pdf. See laboratory website at: http://staff.aist.go.jp/e.yoshida/smaunit/index-e.htm.
893. Swarm-bots Project, Future and Emerging Technologies Program of the European Community; http://www.swarm-bots.org/.
894. Intelligent Autonomous Systems Engineering Laboratory, University of the West of England (UWE), Bristol, U.K.; http://www.ias.uwe.ac.uk/.
895. Josh Bongard, "HYDRA Project," Artificial Intelligence Laboratory, University of Zurich, Switzerland, 19 November 2001; http://www.ifi.unizh.ch/groups/ailab/projects/hydra/.
896. Koji Nishikawa, Takashi Nagai, Nobuyuki Takahashi, "Project: The Development of Amoeba Like Robot," Laboratory of Autonomous Systems Engineering, Complex Systems Engineering, Hokkaido University; http://junji.complex.eng.hokudai.ac.jp/projects/AmoebaRobot/index.html.
897. Random Morphology Robot Project, Department of Computer Science, University of Dortmund, Germany; http://ls11-www.informatik.uni-dortmund.de/alife/rmrobot/.
898. K. Hosokawa, T. Fujii, H. Kaetsu, H. Asama, Y. Kuroda, I. Endo, "Self-organizing collective robots with morphogenesis in a vertical plane," JSME Intl. Journal Series C Mechanical Systems Machine Elements and Manufacturing 42(March 1999):195-202.
899. Dr. Gavin Miller's Snake Robots; http://www.snakerobots.com/main.htm.
900. Ranier Worst, "GMD's collection of snake-like robots caught in the World Wide Web," Institute for Autonomous Intelligent Systems; http://ais.gmd.de/~worst/snake-collection.html.
901. S. Hirose, Biologically Inspired Robots (Snake-like Locomotor and Manipulator), Oxford University Press, Oxford, 1993.
902. P. Menzel, F. D'Aluisio, Robo sapiens: Evolution of a New Species, MIT Press, Cambridge, MA, 2000.
903. Cem Unsal, Han Kiliccote, Pradeep K. Khosla, "I(CES)-Cubes: A modular self-reconfigurable bipartite robotic system," Proc. 1999 SPIE Conf. on Mobile Robots and Autonomous Systems, September 1999, Boston, MA, Sensor Fusion and Decentralized Control in Robotic Systems II, 1999, pp. 258-269; see "I-Cubes": http://www.cs.cmu.edu/~unsal/research/ices/cubes/.
904. Cem Unsal, Pradeep K. Khosla, "Mechatronic design of a modular self-reconfiguring robotic system," Proc. IEEE Intl. Conf. On Robotics and Automation, 2000, pp. 1742-1747.
905. Cem Unsal, Han Kiliccote, Pradeep K. Khosla, "A modular self-reconfigurable bipartite robotic system: Implementation and motion planning," Autonomous Robots 10(2001):23-40.
906. H. Asama et al., eds., Distributed Autonomous Robotic Systems 2, Tokyo, Springer-Verlag, New York, 1996.
907. Research Project, Interaction Lab, USC Robotics Labs; http://www-robotics.usc.edu/~agents/.

908. Y.U. Cao et al, "Cooperative mobile robotics: antecedents and directions," Volume I, Proc. IEEE/RSJ Intl. Conf. On Intelligent Robots and Systems, Pittsburgh PA, August 1995, pp. 226-234.

909. G. Beni, S. Hackwood, "The maximum entropy principle and sensing in swarm intelligence," in F.J. Varela, P. Bourgine, eds., Toward a Practice of Autonomous Systems, MIT Press, Cambridge, MA, 1990, pp. 153-160.

910. S. Hackwood, G. Beni, "Self-organization of sensors for swarm intelligence," Proc. IEEE Intl. Conf. On Robotics and Automation, Nice, France, May 1992, pp. 819-829.

911. Mark M. Millonas, "Swarms, phase transitions, and collective intelligence," in Christopher G. Langton, Artificial Life III, Proc. Volume XVII Santa Fe Institute Studies in the Sciences of Complexity, Addison-Wesley Publishing Company, New York, 1994, p. 417-445.

912. E. Bonabeau, M. Dorigo, G. Theraulaz, Swarm Intelligence: From Natural to Artificial Systems, Santa Fe Institute Sciences of Complexity Series, Oxford University Press, New York, 1999.

913. Eric Bonabeau, Guy Theraulaz, "Swarm smarts," Sci. Amer. 282(March 2000):72-79.

914. "Computer Controlled LEGO® Car Factory," http://vita.bu.edu/cgc/newlego/index.html. See also: C. Cassandras, "Computer Controlled LEGO® Car Factory," University of Massachusetts, 1996; http://web.archive.org/web/20010816195817/http://www.ecs.umass.edu/ece/UG/lego/home.html.

915. Matt Moses, "A Physical Prototype of a Self-Replicating Universal Constructor," Master's Thesis, Department of Mechanical Engineering, University of New Mexico, 2001; http://www.home.earthlink.net/~mmoses152/SelfRep.doc.

916. Thomas Hune, Kim G. Larsen, Paul Pettersson, "Guided Synthesis of Control Programs Using UPPAAL," 20 October 2002, http://www.daimi.au.dk/~baris/CaseStudy/; "A Steel Production Plant Model," LEGO Lab, University of Aarhus, http://legolab.daimi.au.dk/Projects/projects.html.

917. Mitchel Resnick, "LEGO®, Logo, and Life," in Christopher G. Langton, ed., Artificial Life, Santa Fe Institute, Studies in the Science of Complexity, Volume VI, Addison-Wesley, New York, 1989, pp. 397-406.

918. Jonathan B. Knudsen, The Unofficial Guide to LEGO® Mindstorms Robots, O'Reilly & Associates, 1999; Dave Baum, Extreme Mindstorms: An Advanced Guide to LEGO® Mindstorms, APress, 2000; Mario Ferrari, Giulio Ferrari, Ralph Hempel, Building Robots with LEGO® Mindstorms: The Ultimate Tool for Mindstorms Maniacs, Syngress Media Inc., 2001; Mario Ferrari, Giulio Ferrari, Kevin Clague, J.P. Brown, Ralph Hempel, LEGO® Mindstorms Masterpieces: Building Advanced Robots, Syngress Media Inc, 2003; Don Wilcher, LEGO® Mindstorms Mechatronics: Using Systems and Controls to Build Sophisticated Robots, McGraw-Hill/TAB Electronics, New York, 2003.

919. "Erectorworld," http://www.erectorworld.com/.

920. Kendrick Bisset, "Meccano in the United States," 2001; http://www.usmeccano.com/index.html.

921. Alexander Keewatin Dewdney, The Tinkertoy Computer and Other Machinations, W.H. Freeman & Co., San Francisco, CA, 1993. See also: A.K. Dewdney, "A Tinkertoy computer that plays tic-tac-toe," Sci. Amer. 261(October 1989):120-123; http://www.rci.rutgers.edu/~cfs/472_html/Intro/TinkertoyComputer/TinkerToy.html.

922. "A Tinkertoy Page," http://www.constructiontoys.com/store/tinkertoy.html; "Tinkertoy® Construction Sets History," http://www.hasbro.com/pl/page.corporate_history_tinkertoy/dn/default.cfm.

923. Tony Knowles, "Meccano, Erector, Marklin & 500 Other Metal Constructional Toys," http://www.osnl.freeserve.co.uk/.

924. Johan van Dam, "Meccano Imitations," http://www.xs4all.nl/~jvdam/meccano/imi/index_imi.htm.

925. David Williams, "Meccano Imitators," 1996-2002; http://www.freenet.edmonton.ab.ca/meccano/mecimit.html.

926. "The Construction Toy Homepage," http://www.chem.sunysb.edu/msl/lego/homepage.html; Johan van Dam, "Other Construction Toys," http://www.xs4all.nl/~jvdam/meccano/non/index_non.htm; "The Construction Site," http://www.constructiontoys.com/.

927. Hod Lipson, Jordan B. Pollack, "Automatic design and manufacture of robotic lifeforms", Nature 406(2000):974-978; http://golem03.cs-i.brandeis.edu/download/naturegolem.pdf. See also: Rodney Brooks, "From robot dreams to reality," Nature 406(31 August 2000):945-947; George Musser, "Robotics replication: Dawn of a new species?" Sci. Amer. 283(November 2000):26; John Whitfield, "Design for living," Nature Science Update, 31 August 2000; http://www.nature.com/nsu/000831/000831-8.html.

928. "The Golem Project," see: http://www.demo.cs.brandeis.edu/golem/, http://golem03.cs-i.brandeis.edu/index.html, http://golem03.cs-i.brandeis.edu/press.html, http://helen.cs-i.brandeis.edu/golem/.

929. Matthew Fordahl, "Computer makes robot offspring," Associated Press, 30 August 2000, http://www.canoe.ca/CNEWSScience0008/30_robot.html; "Robots making robots, with some help," Science News 158(16 September 2000):189, http://golem03.cs-i.brandeis.edu/press/ScienceNews.pdf; Bruce Sterling, "When robots act like rabbits," Wall Street Journal, 6 September 2000, http://golem03.cs-i.brandeis.edu/press/Wsj_a.jpg; Jennifer Viegas, "Robots self-replicate, team up," Discovery.com News, 30 August 2000, http://golem03.cs-i.brandeis.edu/press/discovery.pdf or http://www.discovery.com/news/briefs/20000830/te_robots.html.

930. Jordan B. Pollack, Hod Lipson, "The GOLEM Project: Evolving Hardware Bodies and Brains," Proceedings of the Second NASA/DoD Workshop on Evolvable Hardware (EH'00), 13-15 July 2000, Palo Alto CA, Institute of Electrical and Electronics Engineers, 2000; http://computer.org/proceedings/eh/0762/07620037abs.htm.

931. For example, see: Terry Wohlers, "The World of Rapid Prototyping," Proc. Fourth Intl. Conf. On Desktop Manufacturing, 24-25 September 1992, San Jose, CA, Wohlers Associates, 1992, http://www.wohlersassociates.com/mr.html; "University Rapid Prototyping Programs," http://home.att.net/~castleisland/u_lks.htm; "Rapid Manufacturing Processes at University and R&D Labs," Carnegie Mellon University, Spring 1997, http://www-2.cs.cmu.edu/People/rapidproto/manufacturing/mfguniversity.html; "The Commercial Rapid Prototyping Systems," http://ecoleing.uqtr.uquebec.ca/geniedoc/gmm/productique/rp_systems.htm; "Commercial Rapid Prototyping System Manufacturers," http://home.att.net/~castleisland/com_lks.htm; "Rapid Prototyping Directory," http://mtiac.iitri.org/pubs/rp/rp6.htm; Stratasys Inc., http://www.stratasys.com; Z Corporation, "Industry-Standard Three-Dimensional Printers & Solutions," http://www.zcorp.com.

932. 3D Systems, "Products"; http://www.3dsystems.com.

933. M. Agarwala, A. Bandyopadhyay, R. van Weeren, V. Jamalabad, P. Whalen, N.A. Langrana, A. Safari,, S.C. Danforth, "Fused deposition of ceramics," J. Rapid Prototyping 2(1996):4-19; Dan Qiu, Noshir A. Langrana, Stephen C. Danforth, "Intelligent toolpath for extrusion-based LM process," http://www.caip.rutgers.edu/~danqiu/sff10.html; "An intelligent CAD system for multi-material layered manufacturing," http://www.caip.rutgers.edu/~danqiu/research.html. See also: Laboratory of Solid Freeform Fabrication of Advanced Ceramics at Rutgers University," http://www.caip.rutgers.edu/sff/; Michael Brooks, "Printing dreams," WorldLink, Magazine of the World Economic Forum, 21 March 2001; http://www.worldlink.co.uk/stories/storyReader$632; "3-D printing technology," New Scientist, 30 September 2000.

934. ToyBuilders.com, a division of Vicale Corp., http://www.toybuilders.com; "Stereolithography (SLA)," http://www.toybuilders.com/stereolithography.htm; "Selective Laser Sintering (SLS)," http://www.toybuilders.com/selective_laser_sintering.htm; "Fused Deposition Modeling (FDM)," http://www.toybuilders.com/fused_deposition_modeling.htm; "Layer Object Manufacturing (LOM)," http://www.toybuilders.com/layer_object_manufacturing.htm; "3 Dimensional Printing (3DP)," http://www.toybuilders.com/3_dimensional_printing.htm.

935. "Fused Deposition Modeling," http://www.quickparts.com/encyclopedia/FDM.pdf; "Info Page: Fused Deposition Modeling," October 1999, http://www-2.cs.cmu.edu/~unsal/research/rapid/fdm.html; "Fused Deposition Modeling," http://www.nitc.qub.ac.uk/divs/adc-fdm.htm; "Fused Deposition Modeling (FDM)," Phoenix Analysis & Design Technologies, 2003, http://www.padtinc.com/rm/fdm/default.htm; "Fused Deposition Modeling," 9 February 2004, http://www.materialise.com/prototypingsolutions/fused_ENG.html.

936. Mark W. Tilden, T.C. Lowe, "Section 6.7.11. The development of useful nanotech robotic systems," in "Chapter 6, Applications: Nanodevices, Nanoelectronics, and Nanosensors," in M.C. Roco, S. Williams, P. Alivisatos, eds., Vision for Nanotechnology Research and Development in the Next Decade, Nanotechnology Research Directions: IWGN Workshop Report, September 1999, p.93; http://www.wtec.org/loyola/nano/IWGN.Research.Directions/chapter06.pdf.

937. M.W. Tilden, M.S. Moses, "Autonomous Self-Assembling Robotic Mechanisms," http://www.winnipegrobotics.com/Pages/Robots/Beam/beam.html; also cited in http://www.wtec.org/loyola/nano/IWGN.Research.Directions/chapter06.pdf (Chapter 6, Section 6.7.11, page 93).

938. M. W. Tilden, “Living Machines and the Robot Jurassic Park: Primitives to Predators,” Neuromorphic Workshop, Telluride, Colorado, July 6, 1995, and Recursos Smithsonian Group, Los Alamos, New Mexico, July 14, 1995.

939. M. W. Tilden, J. Moses, R. Mainieri, and B. Hasslacher, “Autonomous Biomorphic Robots as Platforms for Sensors,” DOE Office of Scientific and Technical Information, Washington, D.C., August 1996; http://solarbotics.net/library/pdflib/pdf/auto_bio_rob_platforms.pdf.

940. M. W. Tilden, “A Concurrent Application Research Proposal for the Development of Living Machines,” NASA AIAA Nanosat Meeting, Houston, Texas, November 1, 1995.

941. Amelie Schmolke, Hanspeter A. Mallot, “Territory formation in mobile robots,” in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 256-259; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub1250.pdf.

942. Gerard K. O’Neill, “The colonization of space,” Physics Today 27(September 1974):32-40; http://www.aeiveos.com/~bradbury/Authors/Engineering/ONeill-GK/TCoS.html.

943. Gerard K. O’Neill, “Space colonies and energy supply to Earth,” Science 190(5 December 1975):941-947.

944. Gerard K. O’Neill, “Space colonies: The high frontier,” The Futurist 10(February 1976):25-33; http://www.aeiveos.com/~bradbury/Authors/Engineering/ONeill-GK/SCTHF.html.

945. Gerard K. O’Neill, The High Frontier, William Morrow, New York, 1977.

946. Freeman J. Dyson, “The life of Gerard K. O’Neill (obituary),” Physics Today 46(February 1993); http://www.ssi.org/obit.html. See also: “Gerard K. O’Neill biography,” Space Frontier Foundation, http://www.space-frontier.org/HighFrontier/gkobio.html.

947. Richard D. Johnson, Charles Holbrow, eds., Space Settlements: A Design Study, NASA/Ames Research Center, NASA SP-413, Washington DC, 1977.

948. T.A. Heppenheimer, Colonies in Space, Warner Books, Inc., New York, 1977.

949. Gerard K. O’Neill, Brian O’Leary, eds., Space-Based Manufacturing from Nonterrestrial Materials, AIAA, New York, 1977.

950. Jerry Grey, ed., Space Manufacturing Facilities I & II, AIAA, New York, 1977.

951. John Billingham, William Gilbreath, Brian O’Leary, eds. Space Resources and Space Settlements, NASA/Ames Research Center, NASA SP-428, Washington DC, 1979.

952. Gerard K. O’Neill, “The low (profile) road to space manufacturing,” Astronautics and Aeronautics 16(March 1978):18-32; available for purchase from SSI at http://www.ssi.org/body_catalog.html.

953. David R. Criswell, “The initial lunar supply base,” in John Billingham, William Gilbreath, Brian O’Leary, eds., Space Resources and Space Settlements, NASA/Ames Research Center, NASA SP-428, Washington DC, 1979, pp. 206-224.

954. Gerard K. O’Neill, “Recent work on use of lunar materials for SPS construction,” Final Proceedings of the Solar Power Satellite Program Review, U.S. Department of Energy, GPO, Washington, DC, 1980.

955. Gerard K. O’Neill, The Technology Edge: Opportunities for America in World Competition, Simon & Schuster, New York, 1984, 1985 (reprint edition).

956. Judson T. Hewitt, personal communication to Robert A. Freitas Jr., 17 March 1997.

957. Judson T. Hewitt, “Development of manufacturing facilities in space able to use only extraterrestrial materials,” Space Power 12(1993):175-227; Judson T. Hewitt, “Construction of solar power satellites and space habitats via self-reproducing manufacturing facilities,” Space Power 13(1994):71-74.

958. “SSI Research Report: First Steps Study,” Space Studies Institute website, April 2003; http://www.ssi.org/body_research.html#systems-first.

959. Space Studies Institute, “First steps to lunar manufacturing: Results of the 1988 SSI Lunar Systems Workshop,” Lunar and Planetary Institute, 1988; available for purchase from SSI at http://www.ssi.org/body_catalog.html.

960. Gerard K. O’Neill, “Alternative plan for U.S. National Space Program,” Space Studies Institute, Princeton, NJ, 1990; http://www.ssi.org/alt-plan.html.

961. David Criswell, Extraterrestrial Materials Processing and Construction, Final Report, NSR 09-051-001, Lunar and Planetary Institute and NASA/Johnson Space Center, Houston TX, 31 January 1980.

962. “Chapter 4. Nonterrestrial Utilization of Materials: Automated Space Manufacturing Facility,” pp. 77-188, and Section 4.3.3, “Starting Kits,” pp. 119-126, in Robert A. Freitas Jr., William P. Gilbreath, eds., Advanced Automation for Space Missions, NASA Conference Publication CP-2255, 1982.

963. Rene H. Miller, Marvin L. Minsky, David B.S. Smith, Space Applications of Automation, Robotics and Machine Intelligence Systems (ARAMIS), Phase I, Final Report, MIT Space Systems Laboratory and AI Laboratory, NASA/Marshall Space Flight Center, NASA CR-162079, August 1982.

964. David L. Akin, Marvin Minsky, Telepresence, ARAMIS (Phase II), MIT Space Systems Laboratory and AI Laboratory, NASA/Marshall Space Flight Center, Contract NAS8-34381, SSL Report #18-83, Phase II Final Report, June 1983.

965. Paul Slysh, Donald A. Kugath, “Large space structure automated assembly technique,” J. Spacecraft 17(July-August 1980):354-362.

966. L.S. Yarbrough, “MSFC Automation R&T Program,” Research and Technology Office, Science and Engineering Directorate, NASA Marshall Space Flight Center, February 1981.

967. “Skyworker,” The Robotics Institute, NASA Grant No. NAG9-1141, 2003; http://www.frc.ri.cmu.edu/projects/skyworker/.

968. Reid Simmons, “Welcome to the Wonderful World of Autonomous Robots!” Robotics Institute, School of Computer Science, Carnegie Mellon University, 11 October 2002; http://www-2.cs.cmu.edu/~reids/.

969. Alberto Behar, George Bekey, George Friedman, “Sub-kilogram intelligent tele-robots for asteroid exploration and exploitation (SKIT),” Space Studies Institute, October-December 1996, pp. 1-10; http://www.ssi.org/SKIT.pdf.

970. C.W. Schneiker, “Prospects and Applications for Genesis and Ultra Mass Production of Sub-Millimeter Machines, Devices, and Replicating Systems,” distributed at 1983 Space Development Conference, Houston, Texas, 1983. Cited in: Conrad Schneiker, “NanoTechnology with Feynman machines: scanning tunneling engineering and artificial life,” in Christopher G. Langton, ed., Artificial Life, Santa Fe Institute, Studies in the Sciences of Complexity, Volume VI, Addison-Wesley, NY, 1989, pp. 443-500. See also: C.W. Schneiker, “Some research topics for a new space development programme,” J. Brit. Interplanet. Soc. 37(1984):190-192.

971. Hans Moravec, “Robots that rove,” Robotics Institute, CMU, 11 September 1984; SIGBIO 7(June 1985):13-15; http://www.frc.ri.cmu.edu/users/hpm/project.archive/general.articles/1985/1985.Omni.html.

972. Steve Vetter, “Minimizing the initial space manufacturing base,” in Barbara Faughnan, ed., Space Manufacturing: 10 Pathways to the High Frontier, Proceedings of the Twelfth SSI-Princeton Conference, 4-7 May 1995, Space Studies Institute, August 1995, pp. 245-253.

973. Tom McKendree, “Planning Scenarios for Space Development,” in Barbara Faughnan, ed., Space Manufacturing: 10 Pathways to the High Frontier, Proceedings of the Twelfth SSI-Princeton Conference, 4-7 May 1995, Space Studies Institute, August 1995, pp. 254-265.

974. Thomas L. McKendree, “Technical and Operational Assessment of Molecular Nanotechnology for Space Operations,” Ph.D. dissertation, University of Southern California, Los Angeles, August 2001.

975. Tom McKendree, “The logical core architecture,” Nanotechnology 9(September 1998):212-222; http://www.foresight.org/Conferences/MNT05/Papers/McKendree/index.html.

976. Thomas L. McKendree, “Balancing molecular nanotechnology-based space transportation and space manufacturing using location theory: a preliminary look,” paper presented at the Space Studies Institute Conference on Space Manufacturing, 8-11 May 1997, http://www.islandone.org/MMSG/ssi97/TMcSSI97.html; Newsletter of the Molecular Manufacturing Shortcut Group, Volume 5, Number 3, Third Quarter, 1997; http://www.islandone.org/MMSG/97sept/.

977. J. Suthakorn, Y. Zhou, G.S. Chirikjian, “Self-replicating robots for space utilization,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002; http://caesar.me.jhu.edu/jackritweb/RoboSphere2002.pdf.

978. Jerome D. Rosen, “Using Mechanosynthetic Assemblers to Build an Orbital Tower,” Newsletter of the Molecular Manufacturing Shortcut Group, Volume 4, Number 1, First Quarter, 1996; http://www.islandone.org/MMSG/9601-news.html#RTFToC46.

979. J. Storrs Hall, “Diamond in the Sky,” IMM Report No. 16, 6 June 2000; http://www.imm.org/Reports/Rep016.html.

980. Gregory S. Chirikjian, Yu Zhou, Jackrit Suthakorn, “Self-replicating robots for lunar development,” JHU Technical Report RMS-1-2002; also in Special Issue on Self-Reconfiguration Robots, ASME/IEEE Transactions on Mechatronics 7(December 2002):462-472; http://caesar.me.jhu.edu/jackritweb/SRR-Mechatronics-Paper.pdf.

981. Alex Ignatiev, T. Kubricht, Alexandre Freundlich, “Solar cell development on the surface of the Moon,” Proc. 49th Intl. Astronautical Congress, IAA-98-IAA. 13.2.03, 1998.

982. Benjamin Chui, Lea Kissner, “Nanorobots for Mars EVA repair,” SAE Intl. Conf. on Environmental Systems, July 2000; http://www.cs.cmu.edu/~leak/ices.pdf.

983. Kenneth Malpass, “Profitable condominium development using self-replicating O’Neill colonies,” in Bettie Greber, ed., Space Manufacturing 13: Settling Circumsolar Space, Proc. Thirteenth SSI/Princeton Conference On Space Manufacturing, 7-9 May 2001, pp. 257-259.

984. Paul D. Fernhout, Cynthia F. Kurtz, “A review of licensing and collaborative development with special attention to design of self-replicating space habitat systems,” in Bettie Greber, ed., Space Manufacturing 13: Settling Circumsolar Space, Proc. Thirteenth SSI/Princeton Conference On Space Manufacturing, 7-9 May 2001, pp. 271-281.

985. Giorgio Buttazzo, “Artificial consciousness: Utopia or real possibility?” IEEE Computer Magazine 34(July 2001):24-30; http://computer.org/computer/co2001/r7024abs.htm (abstract).

986. Ted Howard, “Vision 2020,” http://www.fishnet.co.nz/v2020/visn2020.htm; “Miniature Factory: How do we build a self replicating robotic complex?” http://www.fishnet.co.nz/v2020/minifact.htm; “Doubling is Power,” http://www.fishnet.co.nz/v2020/doubling.htm.

987. Forrest Bishop, “The Starseed/Launcher,” Newsletter of the Molecular Manufacturing Shortcut Group, Volume 4, Number 2, Second Quarter, 1996; http://www.islandone.org/MMSG/9606.html#TofC1.

988. George Friedman, “The Space Studies Institute view on self-replication,” The Assembler 4(Fourth Quarter 1996):1-4; http://www.islandone.org/MMSG/9612.html#TofC1.

989. George Friedman, personal communication to Robert A. Freitas Jr., 22 September 2001.

990. Raj Reddy, “To dream the possible dream,” Commun. ACM 39(May 1996):106-112; http://www.cs.dal.ca/~riordan/CSCI6501/p105-reddy.pdf.

991. A.T. Forrester, J. Perel, J. Mahoney, ‘A critique of the throughput limit in mass spectrographs,” J. Appl. Phys. 49(June 1978):3046-3048.

992. A.L. Vergey, A.K. Yergey, “Preparative scale mass spectrometry: A brief history of the calutron,” J. Amer. Soc. Mass Spectrometry 8(September 1997):943-953; http://masspec.scripps.edu/builders.html. See also: “Episode 2. The Calutron,” Lawrence and His Laboratory, 1981, http://www.lbl.gov/Science-Articles/Research-Review/Magazine/1981/81fepi2.html; “What’s a calutron?” 28 February 1995, http://www.ornl.gov/publications/labnotes/feb95/calutron.html.

993. C.P. Keim, “Enriching stable isotopes electromagnetically,” J. Appl. Phys. 24(October 1953):1255-1261.

994. F.A. White, Mass Spectroscopy in Science and Technology, John Wiley & Sons, New York, 1968.

995. R.G. Wilson, G.R. Brewer, Ion Beams, John Wiley & Sons, New York, 1973.

996. C.A. Robinson, Jr., P.J. Klass, “Technical survey: particle beams, laser weapons,” Aviat. Week Space Technol. 113(28 July 1980)32-66 (Part 1), 113(4 August 1980):44-68 (Part 2).

997. David S. McKay, Hubert P. Davis, Marshall Burns, “Using fabricators to reduce space transportation costs,” Solid Freeform Fabrication Symposium, University of Texas at Austin, 14 August 1995; http://www.ennex.com/publish/199608-MB-SpaceFab.asp.

998. Digital Fabrication Portal “fabbers.com”; http://www.ennex.com/~fabbers/.

999. Brock Hinzmann, “The Personal Factory,” MCB Internet Conference on Rapid Prototyping, 1996; http://www.ennex.com/~fabbers/publish/199600-Brock-PersonalFactory.asp.

1000. Alberto Pique, Douglas B. Chrisey, eds., Direct Write Technologies for Rapid Prototyping Applications: In Sensors, Electronics and Integrated Power Sources, Academic Press, New York, 2001.

1001. Michael Okuda, Denise Okuda, Debbie Mirek, The Star Trek Encyclopedia: A Reference Guide to the Future, Pocket Books, New York, 1994, 1997, 1999 (paperback edition).

1002. Robert A. Freitas Jr., “The future of computers…Replicators,” Analog 116(March 1996):57-73; http://www.rfreitas.com/Nano/TheFutureOfComputers—Analog—March1996.htm#Replicators.

1003. Ronald N. Bracewell, “Communications from Superior Galactic Communities,” Nature, 186, 670-671 (1960). Reprinted in A.C.W. Cameron, ed., Interstellar Communication, W.A. Benjamin, Inc., New York, 1963, pp. 243-248.

1004. Ronald N. Bracewell, “Life in the Galaxy,” in S. T. Butler, H. Messel (eds.), A Journey Through Space and the Atom, Nuclear Research Foundation, Sydney, Australia, 1962. Reprinted in A.C.W. Cameron, ed., Interstellar Communication, W.A. Benjamin, Inc., New York, 1963, pp. 232-242.

1005. Michael A. Arbib, “The likelihood of the evolution of communicating intelligences on other planets,” in Cyril Ponnamperuma, A. G. W. Cameron, eds., Interstellar Communication: Scientific Perspectives, Houghton Mifflin Company, Boston, 1974, pp. 59-78, 65-66.

1006. Arthur C. Clarke, “The Sentinel,” The Avon Science Fiction and Fantasy Reader, 1951.

1007. D.R. Criswell, R.D. Waldron, R. D., “International lunar base and the lunar-based power system to supply Earth with electric power,” Acta Astronautica 29(1993):469-480; David R. Criswell, “Lunar Solar Power System for energy prosperity within the 21st century,” Proc. World Energy Congress, 13-18 September 1998, Houston, TX, Paper 4.1.23, World Energy Council, Washington, D.C., pp. 277-289; D.R. Criswell, “Lunar solar power system: review of the technology base of an operational LSP system,” Acta Astronautica 46(April 2000):531-540; D.R. Criswell, “Solar power via the Moon,” The Industrial Physicist (AIP), April/May 2002, pp. 12-14; D.R. Criswell, “Energy prosperity in the twenty-first century and beyond,” in Innovative Energy Strategies for CO_2 Stabilization, Cambridge University Press, Oxford, 2002.

1008. David R. Criswell, “Chapter 4.11. Solar power system based on the Moon,” in Peter E. Glaser, Frank P. Davidson, Katinka Csigi, eds., Solar Power Satellites: A Space Energy System for Earth, Praxis Publishing Ltd., Chichester, England, 1998, pp. 599-621.

1009. Nikos Prantzos (translated by Stephen Lyle), Our Cosmic Future : Humanity’s Fate in the Universe, Cambridge University Press, 2000; http://www.amazon.com/exec/obidos/tg/detail/-/052177098X/.

1010. N. Metropolis, J. Howlett, G.C. Rota, eds., A History of Computing in the Twentieth Century, Academic Press, New York, 1980.

1011. John von Neumann, “First Draft of a Report on the EDVAC,” Contract No. W-670-ORD-4926 between the United States Army Ordinance Department and the University of Pennsylvania, Moore School of Electrical Engineering, University of Pennsylvania, 30 June 1945; corrected version by Michael D. Godfrey formally published in IEEE Annals of the History of Computing 15(No. 4, 1993):27-75; http://qss.stanford.edu/~godfrey/vonNeumann/vnedvac.pdf and http://instruct1.cit.cornell.edu/courses/sts355/edvac.pdf.

1012. Conrad Schneiker, “NanoTechnology with Feynman machines: scanning tunneling engineering and artificial life,” in Christopher G. Langton, ed., Artificial Life, Santa Fe Institute, Studies in the Sciences of Complexity, Volume VI, Addison-Wesley, NY, 1989, pp. 443-500.

1013. C.W. Schneiker, “NanoTechnology with STMs, Feynman Machines and von Neumann Machines,” poster presented at 1986 Spain STM Conference by Stuart Hameroff, 14-16 July 1986. Cited in: Conrad Schneiker, “NanoTechnology with Feynman machines: scanning tunneling engineering and artificial life,” in Christopher G. Langton, ed., Artificial Life, Santa Fe Institute, Studies in the Sciences of Complexity, Volume VI, Addison-Wesley, NY, 1989, pp. 443-500.

1014. Robert A. Freitas Jr., “A self-reproducing interstellar probe,” J. Brit. Interplanet. Soc. 33(July 1980):251-264.

1015. John D. Barrow, Frank J. Tipler, Chapter 9, The Anthropic Cosmological Principle, Oxford University Press, Oxford, 1986.

1016. Timothy Ferris, “Interstellar spaceflight: Can we travel to other stars?” Scientific American Quarterly (Special Issue: The Future of Space Exploration), Spring 1999, pp. 88-91.

1017. Alex Ellery, “Living Machines,” Astronomy Now (http://www.astronomynow.com/), June 2001.

1018. Michio Kaku, “The physics of extraterrestrial civilizations,” Physics Post, 5 March 2003; http://www.physicspost.com/articles.php?articleId=113&page=4.

1019. Paul Davies, "The Future of Space Exploration," The Australian, 1999; http://abob.libs.uga.edu/bobk/ccc/cc121802.html.
1020. Paul Davies, The Forces of Nature, Cambridge University Press, 1979 (first edition), 1986 (second edition).
1021. C. Sagan, W. Newman, "The Solipsist Approach to Extraterrestrial Intelligence," Q.J.R. Astron. Soc. 24(1983):113-121.
1022. Anthony R. Martin, ed., Project Daedalus: The Final Report on the BIS Starship Study, J. Brit. Interplanet. Soc. Supplement, Unwin Brothers Ltd., London, 1978.
1023. David J. Gingery, Build a Complete Metalworking Shop from Scrap, #2: Build a Metal Lathe, David J. Gingery Publishing, 1983; http://www.lindsaybks.com/dgjp/djgbk/series/index.html; Book No. 177, Lindsay Publications Inc., Bradley, IL, 2002; http://www.lindsaybks.com/dgjp/djgbk/series/index.html.
1024. William K., "Building a Homemade Lathe," MetalWorking GearHeads, 26 February 1998; http://ourworld.compuserve.com/homepages/williamk/Lathe1.htm.
1025. Donald Qualls, "A Homebuilt Metal Cutting Lathe," 2001-2002; http://silent1.home.netcom.com/HomebuiltLathe.htm.
1026. William E. Bradley, "First attempt to define a self-replicating system," June 1980, Appendix 5A, in Robert A. Freitas Jr., William P. Gilbreath, eds., Advanced Automation for Space Missions, NASA Conference Publication CP-2255, 1982, pp. 265-267.
1027. John von Neumann, "Von Neumann's self-reproducing automata," in William Aspray, Arthur Burks, eds., Papers of John von Neumann on Computing and Computer Theory, MIT Press, Cambridge, MA, 1987, pp. 491-552.
1028. Doug Goncz, "ESG Alumni Directory," http://not-the-hub.mit.edu/jrising/alumni.html.
1029. Doug Goncz, 'First attempt at self-reproducing machine tool," Replikon Research, PO Box 4394, Seven Corners, VA 22044-0394, 1997; http://members.aol.com/DGoncz//machine.jpg.
1030. Arthur C. Clarke, Profiles of the Future: An Inquiry Into The Limits of the Possible, Harper and Row Publishers, New York, 1962, p. 221.
1031. C. Maxwell Cade, Other Worlds Than Ours, Taplinger Publishing Co., New York, 1967, pp. 227-228.
1032. Alfred J. Cote Jr., The Search for the Robots, Basic Books, New York, 1967, p. 225.
1033. Roland Puccetti, Persons — A Study of Possible Moral Agents in the Universe, Macmillan & Co., Ltd., London, 1968, p. 48.
1034. Freeman J. Dyson, "The twenty-first century," Vanuxem Lecture delivered at Princeton University, 26 February 1970. (Manuscript courtesy F. Dyson) Revised and reprinted as Chapter 18, "Thought Experiments," in Freeman J. Dyson, Disturbing the Universe, Harper and Row Publishers, New York, 1979, pp. 194-204.
1035. Richard Ofshe, ed., The Sociology of the Possible, Prentice-Hall, Inc., Englewood Cliffs, NJ, 1970, Chapter 14.
1036. P.H.A. Sneath, Planets and Life, Thames and Hudson, London, 1970, pp. 161, 163.
1037. John G. Kemeny, Man and the Computer, Charles Scribner's Sons, New York, 1972, pp. 12-13.
1038. "The vision of John von Neumann," in Adrian Berry, The Next Ten Thousand Years, E. P. Dutton & Co., New York, 1974, Chapter 11.
1039. Cyril Ponnamperuma, A.G.W. Cameron, Interstellar Communication: Scientific Perspectives, Houghton Mifflin Company, Boston, 1974.
1040. Jeremy Bernstein, "When the computer procreates," New York Times Magazine, 15 February 1976, pp. 9, 34-38; "Letters," New York Times Magazine, 21 March 1976, pp. 83-84.
1041. Nigel Calder, Spaceships of the Mind, Viking Press, New York, 1978.
1042. Freeman J. Dyson, Disturbing the Universe, Harper and Row Publishers, New York, 1979.
1043. Chris Boyce, Extraterrestrial Encounter: A Personal Perspective, David & Charles, Newton Abbot, London, 1979.
1044. Frank J. Tipler, "Extraterrestrial intelligent beings do not exist," Q. J. Roy. Astron. Soc. 21(1981):267-282.
1045. Michio Kaku, "The Physics of Extra-Terrestrial Civilizations," Physics Post, 12 June 2003, http://www.physicspost.com/articles.php?articleId=113&page=4; Michio Kaku, "Parallel Universes, the Matrix, and Superintelligence," KurzweilAI.net, 26 June 2003, http://www.kurzweilai.net/meme/frame.html?main=/articles/art0585.html.
1046. Tihamer Nemes, Cybernetic Machines, Gordon and Breach Science Publishers, New York, 1970.
1047. Ewald Heer, "Prospects for robotics in space," Robotics Age l(Winter 1979):20-28.
1048. John C. Beckman, Michael C. Malin, Robert L. Staehle, "Space horizons: A search for potential innovative futures," JPL Publication 500-150, 15 September 1979.
1049. Ewald Heer, "Robots in modern industry," Astronautics and Aeronautics 19(September 1981):50-59.
1050. Carl Sagan, chairman, Machine Intelligence and Robotics: Report of the NASA Study Group, Final Report, NASA TM-82329, March 1980.
1051. Ivan Bekey, John E. Naugle, "Just over the horizon in space," Astronautics and Aeronautics 18(May 1980):64-76.
1052. Riccardo Giacconi, Bernard Oliver, John Carruthers, "Automated manipulating systems," Working Paper of the Telefactors Working Group, Woods Hole New Directions Workshop, 1979.
1053. Robert A. Frosch, personal communication to Robert A. Freitas Jr., 29 August 2003.
1054. Ewald Heer, ed., Proceedings of the Pajaro Dunes Goal-Setting Workshop, unpublished draft notes, June 1980.
1055. Robert A. Frosch, "Future of planetary exploration," lecture delivered at the Commonwealth Club, San Francisco, California, on 14 September 1979.
1056. Timothy J. Healy, James E. Long, "Final Administrative Report, 1980 NASA/ASEE Summer Faculty Technology Feasibility Study, University of Santa Clara — Ames Research Center, NASA TM-82234 (X81-10115), 29 August 1980.
1057. Rodger A. Cliff, "An hierarchical system architecture for automated design, fabrication, and repair," in Jerry Grey, Lawrence A. Hamdan, eds., Space Manufacturing 4, Proceedings of the Fifth Princeton/AIAA/SSI Conference on Space Manufacturing, 18-21 May 1981, Princeton University, AIAA, New York, 1981, pp. 121-126.
1058. "Space agency wants robots to do the work," New Scientist (12 February 1981):410.
1059. "Space: the next 25 years," Mechanical Engineering (February 1981):50-51.
1060. "The seeding of space," Technology Review (February/March 1981):80-81.
1061. Bob Dunnavant, "Robots have to learn about birds and bees," Birmingham Post-Herald, Friday, 27 March 1981, pp. A1-A2.
1062. Steve Butow, Stan Kent, Janet Major, Anthony Matthews, "The getaway special, Part II: flight preparations," Robotics Age (September/October 1983):40-47.
1063. Robert A. Frosch, "Should people, robots, or hybrids operate a space station?" (AAS 83-209), in James D. Burke, April S. Whitt, eds., Space Manufacturing 1983, Volume 53 of Advances in the Astronautical Sciences, Proc. 6th Princeton Conf., American Astronautical Society, 1983, p. 135.
1064. Gregg Maryniak, "Self-replicating machines for space," SSI Update (May/June 1985):2-3; available for purchase from SSI at http://www.ssi.org/body_catalog.html.
1065. "Self-replicating factories in space," in Pioneering the Space Frontier: An Exciting Vision of Our Next Fifty Years in Space, Report of the National Commission on Space, Bantam Books, May 1986, pp. 88-89; http://history.nasa.gov/painerep/part1.html.
1066. Thomas R. McDonough, Space, The Next Twenty-Five Years, John Wiley & Sons, New York, 1987, 1989 (revised edition).
1067. Ralph Merkle, "NASA and self-replicating systems: implications for nanotechnology," Foresight Update No. 9, 30 June 1990, pp. 4-6; http://www.zyvex.com/nanotech/selfRepNASA.html.
1068. J. Doyne Farmer, Alletta d'A. Belin, "Artificial life: the coming evolution," in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 815-840.
1069. Bob Johnstone, "Japan eyes plans for robot-built Moon base," Nature 369(9 June 1994):435. See also: http://www.gcrio.org/ASPEN/epnotes/summaries/368.html.
1070. David F. Noble, The Religion of Technology: The Divinity of Man and the Spirit of Invention, Knopf, New York, 1997.
1071. Editors, Scientific American, Understanding Cloning, Warner Books, New York, 2002.
1072. David Criswell, Peter Marsh, "Working on the Moon," New Scientist (October 1981):30-33.
1073. Vidya S. Taneja, Peter J. Walsh, "Growth considerations of a self-replicating field dependent on external factors," IEEE Trans. on Systems, Man, and Cybernetics 11(August 1981): 558-563.

1074. William B. Zachary, “A feasibility study on the fabrication of integrated circuits and other electronic components in space utilizing lunar materials,” in Jerry Grey, Lawrence A. Hamdan, eds., Space Manufacturing 4, Proceedings of the Fifth Princeton/AIAA/SSI Conference on Space Manufacturing, 18-21 May 1981, Princeton University, AIAA, New York, 1981, pp. 127-131.

1075. Robert A. Freitas Jr., William B. Zachary, “A self-replicating, growing lunar factory,” in Jerry Grey, Lawrence A. Hamdan, eds., Space Manufacturing 4, Proceedings of the Fifth Princeton/AIAA/SSI Conference on Space Manufacturing, 18-21 May 1981, Princeton University, AIAA, New York, 1981, pp. 109-119.

1076. Robert A. Freitas Jr., Timothy J. Healy, James E. Long, “Advanced automation for space missions,” in P.J. Hayes, ed., Proc. 7th International Joint Conference on Artificial Intelligence (IJCAI-81), 24-28 August 1981, Vancouver, Canada, William Kaufmann, Los Altos, CA, 1981, pp. 803-808.

1077. Robert A. Freitas Jr., “Report on the NASA/ASEE summer study on advanced automation for space missions,” J. Brit. Interplanet. Soc. 34(September 1981):407-408.

1078. Robert A. Freitas Jr., Timothy J. Healy, James E. Long, “Advanced automation for space missions,” J. Astronaut. Sci. 30(January-March 1982):1-11.

1079. Robert A. Freitas Jr., “Terraforming Mars and Venus using machine self-replicating systems,” J. Brit. Interplanet. Soc. 36(March 1983):139-142.

1080. Robert A. Freitas Jr., “Roboclone: Self-replicating robots,” Omni 5(July 1983):44-47.

1081. Robert A. Freitas Jr., “Building Athens without the slaves,” Technology Illustrated 3(August 1983):16-20.

1082. Richard Laing, “Artificial organisms: history, problems, directions,” in Christopher G. Langton, ed., Artificial Life, Studies in the Sciences of Complexity, Santa Fe Institute, Volume VI, Addison-Wesley, New York, 1989, pp. 49-61.

1083. Tihamer Toth-Fejel, Tom McKendree, “NSS position paper on space and molecular nanotechnology,” Molecular Manufacturing Shortcut Group (MMSG), Chapter of the National Space Society, 3 January 1997; http://www.islandone.org/MMSG/NSSNanoPosition.html.

1084. John Jefferson Davis, “Artificial Intelligence and the Christian Understanding of Personhood,” Boston Theological Society papers, Boston Theological Institute, 9 November 1998; http://www.bostontheological.org/colloquium/bts/btsdavis2.htm.

1085. David Schrunk, Burton Sharpe, Bonnie Cooper, Madhu Thangavelu, The Moon: Resources, Future Development, and Colonization, John Wiley & Sons, New York, 1999.

1086. Al Globus, “Molecular Nanotechnology in Aerospace: 1999. Replication,” Technical Reports, NAS-00-001, January 2000; http://www.nas.nasa.gov/Research/Reports/Techreports/2000/nas-00-001d.html.

1087. Rolf Pfeifer, “Chapter 7. Self-replication,” in Artificial Life, Univ. Zurich, 2002; http://www.nero.uni-bonn.de/lehreWS02/skript_al_pfeifer_chap7.pdf. See also: R. Pfeifer, H. Kunz, M.M. Weber, D. Thomas, “Chapter 7. Lecture Notes of the Artificial Life,” Department of Information Technology, University of Zurich, 2001; http://www.ifi.unizh.ch/ailab/teaching/AL01/chap7.pdf.

1088. Georg von Tiesenhausen, Wesley A. Darbro, “Self-replicating systems — a systems engineering approach,” Technical Memorandum, Marshall Space Flight Center, Huntsville, Alabama, NASA TM-78304, July 1980.

1089. Francisco Valdes, Robert A. Freitas Jr., “Comparison of reproducing and nonreproducing starprobe strategies for galactic exploration,” J. Brit. Interplanet. Soc. 33(November 1980):402-408.

1090. Wesley A. Darbro, Georg von Tiesenhausen, “Sequences generated by self-replicating systems,” Fibonacci Quarterly 21(March-April 1983):97-106. Also published as: Wesley A. Darbro, Georg von Tiesenhausen, “Sequences generated by self-replicating systems,” NASA/Marshall Space Flight Center, Space Sciences Laboratory preprint series, No. 80-129, December 1980, 20 pp.

1091. Richard L. McCord, “Population control of self-replicating systems,” in 1982 NASA/ASEE Summer Faculty Fellowship Program, NASA/Marshall Space Flight Center, (N83-17386, primary document N83-17359 07-80), NASA CR-162051, NTIS, Washington, DC, August 1982, 12 pp. (Contract No. NASA-NGT-01-002-099).

1092. Richard L. McCord, “Population control of self-replicating systems: Option C,” in 1983 NASA/ASEE Summer Faculty Fellowship Program, NASA/Marshall Space Flight Center, NTIS, Washington, DC, August 1983, 16 pp. (Contract No. NASA-NGT-01-008-021).

1093. Tihamer Toth-Fejel, Self-Test: From Simple Circuits to Self-Replicating Automata, Master’s Thesis, University of Notre Dame, 1984.

1094. Paul B. Dennis, “NASA’s Most Fantastic Proposal Self-Replicating Industry on the Moon by 1999: The classic space exploitation study and petition online”; http://www.harvest-moon.org/aasm/index.htm (original), http://web.archive.org/web/20000831102324/http://www.harvest-moon.org/aasm/index.htm (archive), http://www.virtuallystrange.net/ufo/updates/2000/sep/m20-011.shtml (copy). See also: Paul B. Dennis, “Prohibition Knotwork: The Environmental Crisis and NASA’s Proposal,” December 1999; http://prohibition.knotwork.com/articles/replicators.spider.

1095. “NASA and its Secrets Exposed!” LevyMultiMedia, 1999; http://www.levymultimedia.com/November/1130nasa.htm (original), http://web.archive.org/web/20000623224307/http://www.levymultimedia.com/November/1130nasa.htm (first archive), http://web.archive.org/web/20010417204608/http://www.levymultimedia.com/November/1130nasa.htm (second archive).

1096. Ted Howard, “Welcome to Vision 2020: A possible future for humanity,” Solution-Multipliers Ltd.; http://www.fishnet.co.nz/v2020/index.html.

1097. Dick Teresi, “People: Frosch drops a bomb,” Omni 3(February 1980):119.

1098. Robert A. Frosch, personal communication to Robert A. Freitas Jr., 14 June 1983.

1099. Georg von Tiesenhausen, personal communication to Robert A. Freitas Jr., November 1980.

1100. Charles A. Rosen, “Manufacturing,” in Jerry Grey, Lawrence A. Hamdan, eds., Space Manufacturing 4, Proceedings of the Fifth Princeton/AIAA/SSI Conference on Space Manufacturing, 18-21 May 1981, Princeton University, AIAA, New York, 1981, pp. 13-15.

1101. “Section 5.6.4,” in Robert A. Freitas Jr., William P. Gilbreath, eds., Advanced Automation for Space Missions, NASA Conference Publication CP-2255, 1982, pp. 253-257.

1102. Rodger A. Cliff, “Appendix 5J. Complexity and level of detail in robot programming,” in Robert A. Freitas Jr., William P. Gilbreath, eds., Advanced Automation for Space Missions, NASA Conference Publication CP-2255, 1982, p. 332.

1103. “Figure 7.33. A robot replication facility,” 2001; http://vmc.ppf.ktu.lt/normantas/VEksSistemos/mech_pe8_pve7/Mechatron39.pdf. See in: Richard C. Dorf, Robert H. Bishop, Modern Control Systems 9/E, Prentice-Hall, Upper Saddle River, NJ, 2001; http://cwx.prenhall.com/bookbind/pubbooks/dorf/.

1104. Jeremy D. Dunning, Robert S. Snyder, “Electrophoretic separation of lunar soils in a space manufacturing facility,” in Jerry Grey, Lawrence A. Hamdan, eds., Space Manufacturing 4, Proceedings of the Fifth Princeton/AIAA/SSI Conference on Space Manufacturing, 18-21 May 1981, Princeton University, AIAA, New York, 1981, pp. 371-378.

1105. R.D. Waldron, “Laboratory investigation of HF acid leach process for refining lunar materials: preliminary results,” in Space Manufacturing 1983, Proceedings of the 6th Princeton Conference, American Astronautical Society, Volume 53, Advances in the Astronautical Sciences, 1983.

1106. R.D. Waldron, “Total separation and refinement of lunar soil by the HF acid leach process,” in B. Faughnan, G. Maryniak, eds. Space Manufacturing 5, Proceedings of the 7th Princeton/AIAA/SSI Conference: Engineering with Lunar and Asteroidal Materials, New York, American Institute of Aeronautics and Astronautics, Reston, VA, 1985, pp. 132-149.

1107. Edwin G. Johnsen, “Man, teleoperators, and robots: an optimum team for space exploration,” J. Spacecraft and Rockets 9(July 1972):554-556.

1108. Robert A. Freitas Jr., “An atomic separator for omnivorous self-replicating systems,” unpublished privately circulated document, February 1981, 23 pp, 39 refs.

1109. Steven Hargrove, “Laser technology follows in Lawrence’s footsteps,” Science & Technology Review (May 2000); http://www.llnl.gov/str/Hargrove.html.

1110. Lamont Wood, Rapid Automated Prototyping: An Introduction, Industrial Press, Inc., 1993.

1111. Paul F. Jacobs, Stereolithography and other RP&M Technologies: From Rapid Prototyping to Rapid Tooling, Society of Manufacturing Engineers (SME), 1996; Paul F. Jacobs, Rapid Prototyping and Manufacturing: Fundamentals of StereoLithography, Society of Manufacturing Engineers (SME), 1993.

1112. Ming C. Leu, Handbook of Rapid Prototyping and Layered Manufacturing, Academic Press, New York, 2000.
1113. Kenneth G. Cooper, Rapid Prototyping Technology, Marcel Dekker, New York, 2001.
1114. S.S. Dimov, Duc Truon Pham, Rapid Manufacturing: The Technologies and Applications of Rapid Prototyping and Rapid Tooling, Springer-Verlag, New York, 2001.
1115. L. Lu, J.Y.H. Fuh, Y.S. Wong, Laser-Induced Materials and Processes for Rapid Prototyping, Kluwer Academic Publishers, New York, 2001.
1116. I. Gibson, Software Solutions for Rapid Prototyping, Professional Engineering Publishing, 2002.
1117. Andreas Gebhardt, Rapid Prototyping, Hanser Gardner Publications, 2003.
1118. Chua Chee Kai, Leong Kah Fai, Lim Chu-Sing, Rapid Prototyping: Principles and Applications, Second Edition, World Scientific Publ. Co., New York, 2003.
1119. Steve Upcraft, Paul G. Ranky, Rapid Prototyping Solutions, CIMware USA, Inc., 2003.
1120. "Functional Rapid Prototyping," Cornell Laboratory for Computational Synthesis; http://www.mae.cornell.edu/ccsl/scm/index.htm.
1121. Friedrich B. Prinz et al, "JTEC/WTEC Panel Report on Rapid Prototyping in Europe and Japan," Japanese Technology Evaluation Center, World Technology Evaluation Center, Loyola College in Maryland, March 1997; http://www.wtec.org/loyola/rp/toc.htm.
1122. John D. Madden, Ian W. Hunter, "3-D Micro-fabrication by localized electrochemical deposition," J. Microelectromechanical Systems 5(January-March 1996):24-32; Ian W. Hunter, Serge R. Lafontaine, John D. Madden, "Three dimensional microfabrication by localized electrodeposition and etching," United States Patent No. 5,641,391, 24 June 1997.
1123. "EFAB^{TM}: Rapid Batch Manufacturing of True 3-D Micro-Devices," MEMGen Corp., http://www.isi.edu/efab/; "Technology: Imagine Manufacturing Micromachines Directly From CAD In Days, Not Months," MEMGen Corp., http://www.memgen.com/technology/index.htm.
1124. "MicroFab: Microfabrication through Electrodeposition," 12 October 1998; http://www.thefirst.org/jefft/microfab/index.html.
1125. Guishing Zong, "Solid freeform fabrication using gas phase selective area laser deposition," Ph.D. Dissertation, University of Texas at Austin, August 1991.
1126. Arlan Keith Andrews, "Manufacturing magic," Analog 112(September 1992):60-72.
1127. F. Wallenberger, P. Nordine, M. Boman, "Inorganic fibers and microstructures directly from the vapor phase," Composites Sci. and Technol. 51(1994):193-212; F. Wallenberger, "Inorganic fibers and microfabricated parts by laser assisted chemical vapor deposition (LCVD): Structures and properties," Ceramics Intl. 23(1997):119-126.
1128. Klaus S. Lackner, Christopher H. Wendt, "Exponential growth of large self-reproducing machine systems," Mathl. Comput. Modelling 21(1995):55-81. See also: K.S. Lackner, C.H. Wendt, "Self-reproducing machine systems for global scale projects," Document LA-UR-93-2886, 4th International Conference and Exposition on Engineering, Construction, and Operations in Space/Conference and Exposition/Demonstrations on Robotic for Challenging Environments, Albuquerque, New Mexico, 26 February - 3 March 1994.
1129. Thomas Bass, "Robot, build thyself," Discover (October 1995):64-72; http://208.245.156.153/archive/output.cfm?ID=562.
1130. Matt Moses, personal communication to Robert A. Freitas Jr., 27 August 2003.
1131. Dannie E. Davis, "Autogeneric system," United States Patent No. 4,734,856, 29 March 1988; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,734,856.WKU.&OS=PN/4,734,856.
1132. Glen A. Evans (Egea Biosciences, Inc., San Diego, CA), "Method for the complete chemical synthesis and assembly of genes and genomes," United States Patent No. 6,521,427, 18 February 2003; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,521,427.WKU.&OS=PN/6,521,427. See announcement at: "Egea Granted U.S. Patent Covering Synthetic Genes and Genomes, San Diego, CA, February 25, 2003"; http://www.egeabiosciences.com/022503.htm.
1133. Kinji Mori, Shoji Miyamoto, Hirokazu Ihara, "Cellular type robot apparatus," United States Patent No. 4,608,525, 26 August 1986; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,608,525.WKU.&OS=PN/4,608,525.
1134. Tetsuo Suzuki, "Method and system for controlling robot for constructing products," United States Patent No. 4,835,450, 30 May 1989; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,835,450.WKU.&OS=PN/4,835,450.
1135. Shivadev K. Ubhayakar, Robert D. Baker, "Robotic arm systems," United States Patent No. 4,964,062, 16 October 1990; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,964,062.WKU.&OS=PN/4,964,062.
1136. Shinji Imai, Hiroshi Hamano, Michio Fujinuma, Chikafumi Shimanaka, Shinzo Urushidani, "Production management system and method of transmitting data," United States Patent No. 5,150,288, 22 September 1992; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,150,288.WKU.&OS=PN/5,150,288.
1137. Kazuhiko Yazaki, Hiroyuki Ono, Hiroyuki Kanno, Toru Nishiyama, Minoru Nomaru, "Control for a group of robots," United States Patent No. 5,210,821, 11 May 1993; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,210,821.WKU.&OS=PN/5,210,821.
1138. Kuniya Kaneko, Tsunezi Suzuki, Tadashi Naito, "Control apparatus for an FMS line," United States Patent No. 5,214,588, 25 May 1993; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,214,588.WKU.&OS=PN/5,214,588.
1139. Kermit Aguayo, Khanh Tran, "Automated assembly apparatus," United States Patent No. 5,283,943, 8 February 1994; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,283,943.WKU.&OS=PN/5,283,943.
1140. Larry J. Eshelman, James D. Schaffer, "Method for optimizing the configuration of a pick and place machine," United States Patent No. 5,390,283, 14 February 1995; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,390,283.WKU.&OS=PN/5,390,283.
1141. Nadrian C. Seeman, Yuwen Zhang, "Construction of geometrical objects from polynucleotides," United States Patent No. 5,468,851, 21 November 1995; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,468,851.WKU.&OS=PN/5,468,851.
1142. Jay A. Glaspy Jr., Marta A. Galuga, "Menu driven system for controlling automated assembly of palletized elements," United States Patent No. 5,475,797, 12 December 1995; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,475,797.WKU.&OS=PN/5,475,797.
1143. Daniel Mange, Pierre Marchal, Christian Piguet, Eduardo Sanchez, "Electronic system organized as an array of cells," United States Patent No. 5,508,636, 16 April 1996; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,508,636.WKU.&OS=PN/5,508,636&RS=PN/5,508,636.
1144. Z. Val Kukuljan, George T. Plonski, "Control system and equipment configuration for a modular product assembly platform," United States Patent No. 5,539,975, 30 July 1996; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,539,975.WKU.&OS=PN/5,539,975.
1145. Takuya Nakatani, Mitsutaka Abe, Shigeru Dono, Youji Urano, "Automated part assembly machine," United States Patent No. 5,586,387, 24 December 1996; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,586,387.WKU.&OS=PN/5,586,387.

1146. Seii Miyakawa, Syoji Arimoto, Manabu Ikeda, Toshijiro Ohashi, Minoru Iwata, Mitsuharu Hayakawa, "Automatic manufacturability evaluation method and system," United States Patent No. 5,717,598, 10 February 1998; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,717,598.WKU.&OS=PN/5,717,598.
1147. Gerd Karl Binnig, Heinrich Rohrer, Peter Vettiger, "Mass-storage applications of local probe arrays," United States Patent No. 5,835,477, 10 November 1998; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,835,477.WKU.&OS=PN/5,835,477.
1148. Rondall E. Jones, Randall H. Wilson, Terri L. Calton, "Method and apparatus for automated assembly," United States Patent No. 5,980,084, 9 November 1999; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,980,084.WKU.&OS=PN/5,980,084.
1149. Satoshi Murata, "Universal unit for automatically configuring three-dimensional structures of a desired shape," United States Patent No. 5,988,845, 23 November 1999; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,988,845.WKU.&OS=PN/5,988,845.
1150. E.E. Hui, R.T. Howe, M.S. Rodgers, "Single-Step Assembly of Complex 3-D Microstructures," MEMS 2000, Japan; http://www-bsac.eecs.berkeley.edu/archive/users/hui-elliot/pdf/poppaper.pdf.
1151. Nadrian Seeman, Xiaojun Li, Xiaoping Yang, Jing Qi, "Nanoconstructions of geometrical objects and lattices from antiparallel nucleic acid double crossover molecules," United States Patent No. 6,072,044, 6 June 2000; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,072,044.WKU.&OS=PN/6,072,044.
1152. Michael B. Cohn, Roger T. Howe, "Wafer-to-wafer transfer of microstructures using break-away tethers," United States Patent No. 6,142,358, 7 November 2000 (filed 31 May 1997); http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,142,358.WKU.&OS=PN/6,142,358.
1153. Steven S. Smith, "Construction of nucleoprotein based assemblies comprising addressable components for nanoscale assembly and nanoprocessors," United States Patent No. 6,200,782, 13 March 2001; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,200,782.WKU.&OS=PN/6,200,782.
1154. John C. Eidson, "Constructing applications in distributed control systems using components having built-in behaviors," United States Patent No. 6,205,362, 20 March 2001; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,205,362.WKU.&OS=PN/6,205,362.
1155. Mark H. Yim, "Fault tolerant connection system for transiently connectable modular elements," United States Patent No. 6,233,502, 15 May 2001; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,233,502.WKU.&OS=PN/6,233,502.
1156. David W. Duemler, "Modular automated assembly system," United States Patent No. 6,535,786, 18 March 2003; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,535,786.WKU.&OS=PN/6,535,786.
1157. Jason D. Lohn, Gary L. Haith, Silvano P. Colombano, "Two electromechanical self-assembling systems," presented at the Sixth Foresight Conference on Molecular Nanotechnology, 13-15 November 1998; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/nano1998.pdf or http://ic.arc.nasa.gov/people/jlohn/Papers/nano1998.pdf; pdf version of poster provided to Freitas courtesy of Jason Lohn; http://www.foresight.org/Conferences/MNT6/Abstracts/Lohn/index.html (abstract).
1158. Jason D. Lohn, personal communications to Robert A. Freitas Jr., 22 & 24 September 2001.
1159. Matt Moses, "Self-Replication," 16 December 2002; http://www.home.earthlink.net/~mmoses152/.
1160. N.P. Suh, The Principles of Design, Oxford University Press, Oxford, 1990.
1161. Seth D. Potter, Harvey J. Willenberg, Mark W. Henley, Steven R. Kent, "Architecture options for space solar power," Space Studies Institute, Princeton, NJ, 1999; http://www.ssi.org/Potter_SSP_99_SSI.pdf.
1162. Marshall Burns, Automated Fabrication: Improving Productivity in Manufacturing, Prentice-Hall, 1993.
1163. Jerome L. Johnson, Principles of Computer Automated Fabrication, Palatino Press, 1994.
1164. M.L. Griffith, D.M. Keicher, C.L. Atwood, J.A. Romero, J.E. Smugeresky, L.D. Harwell, D.L. Greene, "Freeform Fabrication of Metallic Components Using Laser Engineered Net Shaping (LENS)," in D.L. Bourell, J.J. Beaman, H.L. Marcus, R.H. Crawford, J.W. Barlow, eds., Solid Freeform Fabrication Proceedings, The University of Texas at Austin, August 1996, pp. 125-132.
1165. D. Krantz et. al., "On-Demand Spares Fabrication During Space Missions Using Laser Direct Metal Deposition," in M.S. El-Genk, Space Technology and Applications International Forum 2001, American Institute of Physics, 2001.
1166. Evan Malone, personal communication to Robert A. Freitas Jr., 4 September 2003.
1167. O. Chocron, P. Bidaud, "Genetic design of 3-D modular manipulators," Proc. 1997 IEEE Intl. Conf. on Robotics and Automation, Vol. 1, 1997, pp. 223-228.
1168. Peter Dittrich, A. Burgel, Wolfgang Banzhaf, "Learning to move a robot with random morphology," in P. Husbands, J.A. Meyer, eds., Evolutionary Robotics: First European Workshop, EvoRobot98, Springer-Verlag, 1998.
1169. "Dimension 3-D Printer Featured as Part of Exploratorium Museum's TeleSculpture 2003 Exhibit," Business Wire, 10 October 2003; http://home.businesswire.com/portal/site/google/index.jsp?ndmViewId=news_view&newsId=20031010005389&newsLang=en.
1170. Evan Malone, Kian Rasa, Daniel Cohen, Todd Isaacson, Hilary Lashley, Hod Lipson, "Freeform fabrication of 3-D zinc-air batteries and functional electro-mechanical assemblies," Proc. 14th Conference on Solid Freeform Fabrication, Austin TX, Aug 2003, Rapid Prototyping Journal 10(2004):58-69.
1171. Christopher J. Phoenix, "Partial design for macro-scale machining self-replicator," posted 3 March 1998 to sci.nanotech; http://discuss.foresight.org/critmail/sci_nano_tech/0415.html.
1172. Mike Collins, Masters Thesis Project, Department of Mechanical and Aerospace Engineering, University of Florida; personal communication to Robert A. Freitas Jr., 15 October 2003.
1173. Saul Griffith, "Towards Personal Fabricators: Tabletop tools for micron and sub-micron scale functional rapid prototyping," Master's Thesis in Media Arts and Science, Massachusetts Institute of Technology, February 2001, 81pp; http://web.media.mit.edu/~saul/mlmasters/sm_masters.pdf. See also: "Presentation and perspectives on personal fabrication," http://web.media.mit.edu/~saul/pf/pf.ppt.
1174. Victor Papanek, Design for the Real World: Human Ecology and Social Change, Second Edition, Van Nostrand Reinhold, New York, 1984; Victor Papanek, The Green Imperative: Ecology and Ethics in Design and Architecture, Thames and Hudson, New York, 1995.
1175. Brent A. Ridley, B. Nivi, Joseph M. Jacobson, "All-inorganic field effect transistors fabricated by printing," Science 286(22 October 1999):746-749; http://www.media.mit.edu/molecular/Science10-99.pdf.
1176. Stephen Mihm, "Print your next PC," Technology Review, November/December 2000; http://www.techreview.com/articles/nov00/mihm_printable.htm.
1177. Sawyer B. Fuller, Eric J. Wilhelm, Joseph M. Jacobson, "Ink-jet printed nanoparticle microelectromechanical systems," J. Microelectromechanical Systems 11(January-March 2002):54-60; http://www.media.mit.edu/molecular/IEEE-MEMS2-02.pdf. See also: S. Fuller, J. Jacobson, "Ink jet fabricated nanoparticle MEMS," in Proc. IEEE Microelectromech. Syst. Conf., 2000, pp. 138-141; Joseph Jacobson, Eric Wilhelm, Colin Bulthaup, Brent Ridley, "Nanotectonics: Fabrication of inorganic transistors and micro-electro-mechanical systems from nanoparticle building blocks," paper H8.6, Session H8: Fabrication and Properties of 3D-ordered Nanostructures, Symposium on Three-Dimensional Nanoengineered Assemblies, 1-5 December 2002, Materials Research Society (www.mrs.org) Symposium Proceedings, Vol. 739, 2003. See also: Sawyer B. Fuller, "Ink jet deposition of inorganic nanoparticle materials as a route to desktop fabrication of integrated logic and micromachinery," Thesis, B.S. Mech. Eng., MIT, June 2000.

1178. K.F. Teng, R.W. Vest, “A microprocessor-controlled ink jet printing system for electronic circuits,” IEEE Trans. Indust. Electron. 35(1988):407-412.

1179. “Application of ink jet technology on photovoltaic metallization,” IEEE Electron Device Lett. 9(November 1988):591-592.

1180. T.R. Hebner, C.C. Wu, D. Marcy, M.H. Lu, J.C. Sturm, “Ink-jet printing of doped polymers for organic light emitting devices,” Appl. Phys. Lett. 72(1998):519-521.

1181. G. Percin, T.S. Lundgren, B.T. Khuri-Yakub, “Controlled ink-jet printing and deposition of organic polymers and solid particles,” Appl. Phys. Lett. 73(1998):2375-2377.

1182. J. Bharathan, Y. Yang, “Polymer electroluminescent devices processed by inkjet printing: I. Polymer light-emitting logo,” Appl. Phys. Lett. 72(1998):2660-2662.

1183. D.J. Hayes, W.R. Cox, M.E. Grove, “Microjet printing of polymers and solder for electronics manufacturing,” J. Electron. Manufact. 8(1998):209-216.

1184. B. Comiskey, J.D. Albert, H. Yoshizawa, J. Jacobson, “An electrophoretic ink for all-printed reflective electronic displays,” Nature 394(1998):253-255.

1185. John Markoff, “Innovation at Hewlett Tries to Evade the Ax,” The New York Times, 5 May 2003, p. C1; http://www.nytimes.com/2003/05/05/technology/05HEWL.html?th or http://query.nytimes.com/gst/abstract.html?res=F30711FC38580C768CDDAC0894DB404482.

1186. “Printed Machines,” http://www.media.mit.edu/molecular/projects.html.

1187. John Canny’s Home Page; http://www.cs.berkeley.edu/~jfc/.

1188. John Canny, Jeremy Risner, Vivek Subramanian, “Flexonics: Printable flexure-based mechatronic devices,” WAFR, 15-17 December 2002, Nice, France; http://www.cs.berkeley.edu/~risnerj/wafr2002_presentation6.ppt. See also: D. Huang, F. Liao, S. Molesa, D. Redinger, V. Subramanian, “Plastic-compatible low resistance printable gold nanoparticle conductors for flexible electronics,” J. Electrochem. Soc. 150(2003):412-417; http://www-device.eecs.berkeley.edu/~viveks/Papers/412ECS150.pdf.

1189. “Gadget printer promises industrial revolution,” New Scientist, 8 January 2003; http://www.newscientist.com/news/news.jsp?id=ns99993238.

1190. Daithi Ohanluain, “3-D Printing’s Great Leap Forward,” Wired, 11 August 2003; http://wired.com/news/technology/0,1282,59648,00.html.

1191. Rolltronics Inc.; http://www.rolltronics.com.

1192. Z Corporation website; http://www.zcorp.com. See also: Z Corporation Releases Z®406 3D Color Printer,” 15 May 2001; http://www.zcorp.com/content/newsroom/print/Z406.html.

1193. Sara McMains, Jordan Smith, Carlo Sequin, “The evolution of a layered manufacturing interchange format,” Proc. 2002 ASME Design Engineering Technical Conferences (DETC02), 29 September 2002, Montreal, Canada, Paper DETC2002/DAC-34136; http://www.me.berkeley.edu/~mcmains/DETC02DAC34136.pdf.

1194. James E. Smay, Joseph Cesarano III, Jennifer A. Lewis, “Colloidal inks for directed assembly of 3-D periodic structures,” Langmuir 18(2002):5429-5437; http://colloids.mse.uiuc.edu/research/langmuir_article.pdf. See also: James E. Smay, Jennifer A. Lewis, “Colloidal inks for directed assembly of 3-D periodic structures,” Paper SL2, 74th Annual Meeting, The Society of Rheology, October 2002; http://www.rheology.org/sor02a/abstract.asp?PaperID=243.

1195. Vijay K. Varadan, Xiaoning Jiang, Vasundara V. Varadan, Microstereolithography and other Fabrication Techniques for 3-D MEMS, John Wiley & Sons, New York, 2001.

1196. http://dmtwww.epfl.ch/~abertsch/bibliography.html.

1197. Charles W. Hull, “Apparatus for production of three-dimensional objects by stereolithography,” United States Patent No. 4,575,330, 11 March 1986; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,575,330.WKU.&OS=PN/4,575,330.

1198. K. Yamaguchi, T. Nakamoto, “Consideration on the optimum conditions to produce micromechanical parts by photo polymerization using direct focused beam writing,” Proc. 6th Intl. Symp. on Micro Machine and Human Science (MHS’95), 1995, pp. 71-76.

1199. T. Nakamoto, K. Yamaguchi, P.A. Abraha, K. Mishima, “Manufacturing of three-dimensional micro-parts by UV laser induced polymerization,” J. Micromech. Microeng. 6(1996):240-253.

1200. A. Bertsch, S. Zissi, J.Y. Jezequel, S. Corbel, J.C. Andre, “Microstereophotolithography using a liquid crystal display as dynamic mask-generator,” Micro. Tech. 3(1997):42-47.

1201. M. Cabrera, A. Bertsch, J. Chassaing, J.Y. Jezequel, J.C. Andre, “Microfabrication of very small objects: pushing the limits of stereophotolithography,” Mol. Cryst. Liq. Cryst. 315(1998):223-234.

1202. C. Ecoffet, A. Espanet, D.J. Lougnot, “Photopolymerization by evanescent waves: a new method to obtain nanoparts,” Adv. Mater. 10(1998):411-414.

1203. K. Ikuta, S. Maruo, S. Kojima, “New micro stereo lithography for freely movable 3-D micro structure — Super IH Process with submicron resolution,” Proc. 11th IEEE Workshop on Micro Electro Mechanical Systems (MEMS’98), 1998, pp. 290-295.

1204. S. Maruo, S. Kawata, “Two-photon-absorbed near-infrared photopolymerization for three-dimensional microfabrication,” J. Microelectromechanical Syst. 7(1998):411-415.

1205. D. Pede, G. Serra, D. De Rossi, “Microfabrication of conducting polymer devices by ink-jet stereolithography,” Mater. Sci. Eng. C 5(1998):289-291.

1206. X. Zhang, X.N. Jiang, C. Sun, “Micro-stereolithography for MEMS,” Micro Electro Mechanical Systems (MEMS) ASME 66(1998):3-9.

1207. C.R. Chatwin, M. Farsari, S. Huang, M.I. Heywood, R.C.D. Young, P.M. Birch, F. Clarte-Tournier, J.D. Richardson, “Characterization of epoxy resins for microstereolithographic rapid prototyping,” Int. J. Adv. Manuf. Technol. 15(1999):281-286.

1208. S. Maruo, K. Ikuta, “Movable microstructures made by two-photon three dimensional microfabrication,” Proc. Intl. Symp. on Micromechatronics and Human Science (MHS’99), 1999, pp. 173-178.

1209. J.S. Young, S.R. Fox, K.S. Anseth, “A novel device for producing three-dimensional objects,” J. Manufacturing Sci. and Eng. — Transactions of the ASME 121(1999):474-477.

1210. X. Zhang, X. Jiang, C. Sun, “Micro-stereolithography of polymeric and ceramic microstructures,” Sensors and Actuators A 77(1999):149-156.

1211. A. Bertsch, P. Bernhard, C. Vogt, P. Renaud, “Rapid prototyping of small size objects,” Rapid Prototyping Journal 6(2000):259-266.

1212. M. Farsari, F. Clarte-Tournier, S. Huang, C.R. Chatwin, D. Budgett, P.M. Birch, R.C.D. Young, J.D. Richardson, “A novel high-accuracy microstereolithography method employing an adaptive electro-optic mask,” J. Mater. Process. Technol. 107(2000):167-172.

1213. P. Galajda, O. Pal, “Complex micromachines produced and driven by light,” Appl. Phys. Lett. 78(2001):249-251.

1214. S. Monneret, C. Provin, H. Le Gall, “Micro-scale rapid prototyping by stereolithography,” Proc. 8th IEEE Intl. Conf. on Emerging Technologies and Factory Automation (ETFA 2001) 2(2001):299-304.

1215. C. Provin, S. Monneret, “Complex ceramic-polymer composite microparts made by microstereolithography,” Proc. Design, Test, Integration and Packaging of MEMS/MOEMS Conf., SPIE 4408(2001):535-542.

1216. S. Maruo, K. Ikuta, “Submicron stereolithography for the production of freely movable mechanisms by using single-photon polymerization,” Sensors and Actuators A 100(2002):70-76.

1217. C. Sun, X. Zhang, “Experimental and numerical investigations on microstereolithography of ceramics,” J. Appl. Phys. 92(2002):4796-4802.

1218. Dongmin Wu, Nicholas Fang, Cheng Sun, Xiang Zhang, “Adhesion force of polymeric three-dimensional microstructures fabricated by microstereolithography,” Appl. Phys. Lett. 81(2002):3963-3965.

1219. A. Bertsch, S. Jiguet, P. Bernhard, P. Renaud, “Microstereolithography: a review,” Mat. Res. Soc. Symp. Proc. 739(2003):LL1.1.1-LL1.1.11.

1220. S. Maruo, K. Ikuta, H. Korogi, “Submicron manipulation tools driven by light in a liquid,” Appl. Phys. Lett. 82(2003):133-135.

1221. S. Maruo, K. Ikuta, H. Korogi, “Optically driven micromanipulation tools fabricated by two-photon microstereolithography,” Mat. Res. Soc. Symp. Proc. 739(2003):H9.4.1-H9.4.6.

1222. A. Bertsch, S. Zissi, M. Calin, S. Ballandras, A. Bourjault, D. Hauden, J.C. Andre, “Conception and realization of miniaturized actuators fabricated by microstereophotolithography and actuated by shape memory alloys,” Proc. 3rd France-Japan Congress and 1st Europe-Asia Congress on Mechatronics 2(1996):631-634.

1223. S. Ballandras, M. Calin, S. Zissi, A. Bertsch, J.C. Andre, D. Hauden, “Microstereophotolithography and shape memory alloy for the fabrication of miniaturized actuators,” Sensors and Actuators A 62(1997):741-747.

1224. K. Ikuta, “Biomedical micro device fabricated by micro stereo lithography (IH process) ‘Metabiotic Device’ — a synthetic approach for life science,” Proc. 6th Intl. Symp. on Micro Machine and Human Science (MHS’95), 1995, pp. 71-76.

1225. K. Ikuta, Y. Sasaki, H. Maegawa, S. Maruo, T. Hasegawa, "Micro ultrasonic homogenizer chip made by hybrid microstereolithography," Proc. Micro Total Analysis Systems Conference (MicroTAS'02) 2(2002):745-747.

1226. T.S. Ji, K.J. Vinoy, V.K. Varadan, "Distributed MEMS phase shifters by microstereolithography on silicon substrates for microwave and millimeter wave applications," Smart Materials and Structures 10(2001):1224-1229.

1227. Y. Mizukami, D. Rajniak, M. Nishimura, "An integrated micro-electrophoretic chip fabricated using a new stereolithographic process," Proc. 13th IEEE Intl. Conf. on Micro Electro Mechanical Systems (MEMS 2000), 2000, pp. 751-756.

1228. J. Cooper McDonald, M.L. Chabinyc, S.J. Metallo, J.R. Anderson, G.M. Whitesides, "Prototyping of microfluidic devices in poly(dimethylsiloxane) using solid-object printing," Anal. Chem. 74(2002):1537-1545.

1229. Daniel Therriault, Scott R. White, Jennifer A. Lewis, "Chaotic mixing in three-dimensional microvascular networks fabricated by direct-write assembly," Nat. Mater. 2(April 2003):265-271 (doi:10.1038/nmat863), Nat. Mater. 2(May 2003):347 (erratum); http://www.nature.com/cgi-taf/DynaPage.taf?file=/nmat/journal/v2/n4/abs/nmat863.html (abstract). See also: James E. Kloeppel, "Fabricated microvascular networks could create compact fluidic factories," News Bureau, University of Illinois at Urbana-Champaign, 24 March 2003; http://www.news.uiuc.edu/scitips/03/0324microvascular.html.

1230. S. Maruo, K. Ikuta, T. Ninagawa, "Multi-polymer microstereolithography for hybrid opto-MEMS," Proc. 14th IEEE Intl. Conf. on Micro Electro Mechanical Systems (MEMS 2001), 2001, pp. 151-154.

1231. M.C. Carrozza, N. Croce, B. Magnani, P. Dario, "A piezoelectric-driven stereolithography-fabricated micropump," J. Micromech. Microeng. 5(1995):177-179.

1232. D. Accoto, M.C. Carrozza, P. Dario, "Modelling of micropumps using unimorph piezoelectric actuators and ball valves," J. Micromech. Microeng. 10(2000):277-281.

1233. V.K. Varadan, V.V. Varadan, "Micro pump and venous valve by micro stereo lithography," Proc. SPIE Smart Structures and Materials 2000: Smart Electronics and MEMS 3990(2000):246-254.

1234. M. Calin, A. Bertsch, N. Chaillet, S. Zissi, S. Ballandras, J. C. Andre, A. Bourjault, D. Hauden, "Microrobots realized by microstereophotolithography and actuated by shape memory alloys," Proc. 1997 IEEE/RSJ International Conference on Intelligent Robot and Systems 3(1997):V33-V34.

1235. L. Nelson, N. Richardson, "Formation of thin rods of pyrolytic carbon by heating with a focused carbon dioxide laser," Materials Res. Bull. 7(1972):971-976.

1236. H. Westberg, M. Boman, S. Johansson, J. Schweitz, "Truly three dimensional structures microfabricated by laser chemical processing," IEEE, May 1991, pp. 516-519; S. Johansson, J. Schweitz, H. Westberg, M. Boman, "Microfabrication of three-dimensional boron structures by laser chemical processing," J. Appl. Phys. 72(15 December 1992):5956-5963.

1237. J. Maxwell, K. Larsson, M. Boman, P. Hooge, K. Williams, P. Coane, "Rapid prototyping of functional three-dimensional microsolenoids and electromagnets by high-pressure laser chemical vapor deposition," Solid Freeform Fabrication, August 1998, pp. 529-536; J. Maxwell, M. Boman, K. Williams, K. Larsson, N. Jaikumar, G. Saiprasanna, "High-speed laser chemical vapor deposition of amorphous carbon fibers, stacked conductive coils, and folded helical springs," SPIE Conf. on Micromachining and Microfabrication Process Technology V, Santa Clara, CA, September 1999, SPIE, Vol. 3874, pp. 227-235; K. Williams, J. Maxwell, K. Larsson, M. Boman, "Freeform fabrication of functional microsolenoids, electromagnets and helical springs using high-pressure laser chemical vapor deposition," IEEE, 1999, pp. 232-237.

1238. D. Messia, J. Pegna, W.H. Lee, "Layered micro-wall structures from gas phase," Proc. Solid Freeform Fabrication Symposium, August 1997, pp. 231-240.

1239. Chad E. Duty, Daniel L. Jean, W. Jack Lackey, "Laser CVD rapid prototyping," Proc. Amer. Ceramic Soc. Meeting, Cocoa Beach, FL, January 1999, pp. 347-354; Daniel L. Jean, Chad E. Duty, Brian T. Fuhrman, W. Jack Lackey, "Precision LCVD system design with real time process control," Proc. Solid Freeform Fabrication Symposium, Austin, TX, August 1999, pp. 59-65; Daniel L. Jean, Chad E. Duty, Brian T. Fuhrman, W. Jack Lackey, "Precision carbon deposition using pyrolytic laser chemical vapor deposition (LCVD)," http://www.me.gatech.edu/Lackey/djsff2000.pdf.

1240. S. Kawata, H.-B. Sun, T. Tanaka, K. Takada, "Finer features for functional microdevices," Nature 412(2001):697-698.

1241. W.C. Wilson Jr., T. Boland, "Cell and organ printing 1: Protein and cell printers," Anat. Rec. 272A(June 2003):491-496.

1242. T. Boland, V. Mironov, A. Gutowska, E.A. Roth, R.R. Markwald, "Cell and organ printing 2: Fusion of cell aggregates in three-dimensional gels," Anat. Rec. 272A(June 2003):497-502.

1243. Vladimir Mironov, Thomas Boland, T. Trusk, G. Forgacs, R.R. Markwald, "Organ printing: computer-aided jet-based 3-D tissue engineering," Trends Biotechnol. 21(April 2003):157-161.

1244. Charles Choi, "Ink-jet printing creates tubes of living tissue," New Scientist, 22 January 2003; http://www.newscientist.com/news/print.jsp?id=ns99993292.

1245. L.R. Bao, X. Cheng, X.D. Huang, L.J. Guo, S.W. Pang, A.F. Yee, "Nanoimprinting over topography and multilayer three-dimensional printing," J. Vac. Sci. Technol. B 20(2003):2881.

1246. John Whitfield, "Bull wins size prize," Nature Science Update, 16 August 2001; http://www.nature.com/nsu/010816/010816-16.html.

1247. Seth R. Marder, Joseph W. Perry, "Two-photon materials chemistry," 11th Foresight Conference on Molecular Nanotechnology, October 2003; http://www.foresight.org/Conferences/MNT11/Abstracts/Marder/index.html. See also: Focal Point Microsystems LLC.

1248. Robert Riehn, Ana Charas, Jorge Morgado, F. Cacialli, "Near-field optical lithography of a conjugated polymer," Appl. Phys. Lett. 82(27 January 2003):526-528; http://www.aidic.it/op2003/opwebpapers/9%20Riehn.pdf. See also: "Nano rapid prototyping advances," TRNmag.com, 18/25 June 2003; http://www.trnmag.com/Stories/2003/061803/Nano_rapid_prototyping_advances_Brief_061803.html.

1249. O. Lehmann, M. Stuke, "Laser-driven movement of three-dimensional microstructures generated by laser rapid prototyping," Science 270(1995):1644-1646.

1250. T. Gotz, M. Stuke, "Short pulse UV laser ablation of solid and liquid metals," Appl. Phys. A64(1997):539-543.

1251. M.C. Wanke, O. Lehmann, K. Muller, Q. Wen, M. Stuke, "Laser rapid prototyping of photonic band-gap microstructures," Science 275(1997):1284-1286.

1252. Duncan Graham-Rowe, "Bad breaks fixed fast by bone 'printer'," NewScientist.com, 20 June 2003, http://www.newscientist.com/news/news.jsp?id=ns99993844; "The Plasti-Bone: A Ceramic Polymer Innovation In Medicine," Office of Naval Research (ONR) Media, 13 June 2003, http://www.onr.navy.mil/media/print_tipoff_display.asp?ID=43 or http://www.sciencedaily.com/releases/2003/06/030616090308.htm.

1253. Therics, Inc.; http://www.therics.com.

1254. Sciperio Inc., "Human Architectural Tool (HAT) Capabilities," 2003; http://www.sciperio.com/bio/hat.html.

1255. Hesham Taha, Robert S. Marks, Levi A. Gheber, Ittay Rousso, John Newman, Chaim Sukenik, Aaron Lewis, "Protein printing with an atomic force sensing nanofountainpen," Appl. Phys. Lett. 83(2003):1041.

1256. Aristides Docoslis, Paschalis Alexandridis, "One-, two-, and three-dimensional organization of colloidal particles using non-uniform AC electric fields" Electrophoresis 23(2002):2174-2183. See also: John Della Contrada, "UB Engineer Develops Novel Method for Assembly of Nanoparticles. Process may lead to manufacture of nanoscale devices," University at Buffalo, The State University of New York, 21 November 2002; http://www.buffalo.edu/news/fast-execute.cgi/article-page.html?article=59620009.

1257. "Personal Fabrication: A Talk with Neil Gershenfeld," Edge 123, 24 July 2003; http://www.edge.org/documents/archive/edge123.html or http://www.kurzweilai.net/meme/frame.html?main=/articles/art0601.html.

1258. "Robot learns to reproduce," BBC News, 30 August 2000; http://news.bbc.co.uk/1/hi/sci/tech/903238.stm.

1259. Curt Bererton, Ph.D. "Research" page, Dept. of Computer Science, Carnegie Mellon University, 2003; http://www-2.cs.cmu.edu/~curt/research.html#publications.

1260. Curt Bererton, Pradeep Khosla, "Towards A Team of Robots with Repair Capabilities: Docking Systems," Proc. Intl. Symp. on Experimental Robotics, 2000; http://www-2.cs.cmu.edu/~curt/ISER_Final_V2.htm.

1261. Curt Bererton, Pradeep Khosla, "Towards A Team of Robots with Reconfiguration and Repair Capabilities," Proc. IEEE Intl. Conf. on Robotics and Automation (ICRA 2001), Vol. 3, 2001, pp. 2923-2928; http://www-2.cs.cmu.edu/~curt/ICRA2001_FinalPrint.htm.

1262. Curt Bererton, Pradeep Khosla, "An analysis of cooperative repair capabilities in a team of robots," Proc. IEEE Intl. Conf. on Robotics and Automation (ICRA 2002), Vol. 1, 2002, pp. 476-482; http://www-2.cs.cmu.edu/~curt/ICRA2002/ICRA2002_FinalPrint_ps.ps.

1263. Curt Bererton, repair robot videos: "Teleoperation of the repair robot" (18 Meg avi), http://www-2.cs.cmu.edu/~curt/Videos/Repair_Robot_Teleoperation.avi; "Autonomous docking using vision" (4 Meg avi), http://www-2.cs.cmu.edu/~curt/Videos/Repair_Robot_Visual_Docking.avi; "Autonomous module removal using vision" (18 Meg avi), http://www-2.cs.cmu.edu/~curt/Videos/Visual_Module_Removal_Bad.avi.

1264. A.M. Flynn, R.A. Brooks, W.M. Wells III, D.S. Barrett, "Intelligence for miniature robots," Intl. J. Sensors Actuators 20(December 1989):187-196.

1265. R.A. Brooks, "Intelligence without representation," Artificial Intelligence Journal 47(1991):139-159; http://www.ai.mit.edu/people/brooks/papers/representation.pdf.

1266. R.A. Brooks, "New approaches to robotics," Science 253(September 1991):1227-1232; http://www.ai.mit.edu/people/brooks/papers/new-approaches.pdf.

1267. Luc Steels, Rodney A. Brooks, eds., The Artificial Life Route to Artificial Intelligence: Building Embodied Situated Agents, Lawrence Erlbaum Associates, Hillsdale, NJ, 1995.

1268. Cynthia Breazeal, Designing Sociable Robots, Cambridge, MA, 2001; B. Adams, Cynthia Breazeal, Rodney A. Brooks, Brian Scassellati, "Humanoid robots: A new kind of tool," IEEE Intelligent Systems and Their Applications: Special Issue on Humanoid Robotics 15(July/August 2000):25-31; http://www.ai.mit.edu/people/brooks/papers/IEEE-cog.pdf.

1269. Rodney Allen Brooks, Flesh and Machines: How Robots Will Change Us, Pantheon Books, New York, 2002.

1270. "Hannibal and Attila"; http://www.ai.mit.edu/projects/hannibal/hannibal.html.

1271. Rodney Brooks, Cambrian Intelligence: The Early History of the New AI, MIT Press, Cambridge, MA, 1999.

1272. "Genghis"; http://www.ai.mit.edu/projects/genghis/genghis.html.

1273. "Cog"; http://www.ai.mit.edu/projects/humanoid-robotics-group/cog/; Rodney A. Brooks, Cynthia Breazeal, Matthew Marjanovic, Brian Scassellati, Matthew Williamson, "The Cog project: Building a humanoid robot," in C. Nehaniv, ed., Computation for Metaphors, Analogy, and Agents: Lecture Notes in Artificial Intelligence 1562, Springer, New York, 1999, pp. 52–87; http://www.ai.mit.edu/people/brooks/papers/CMAA-group.pdf; R.A. Brooks, "The Cog project," J. Robotics Soc. Japan (Toshihiro Matsui, ed., Special Issue (Mini) on Humanoid) 15(October 1997); see also: "The Humanoid Robotics Group," http://www.ai.mit.edu/projects/humanoid-robotics-group/.

1274. "Kismet"; http://www.ai.mit.edu/projects/humanoid-robotics-group/kismet/.

1275. Rodney A. Brooks, "Living machines," MIT AI Lab Research Abstracts, September 2001; http://www.ai.mit.edu/projects/living-machines/publications/rod-brooks-abstract2001.pdf.

1276. Rodney Brooks, "The relationship between matter and life," Nature 409(18 January 2001):409-411; http://www.ai.mit.edu/projects/living-machines/publications/nature.pdf.

1277. John Brockman, "Beyond computation: A talk with Rodney Brooks," Edge Foundation, Inc., 5 June 2002; http://www.edge.org/3rd_culture/brooks_beyond/beyond_print.html.

1278. Jessica Banks, "Progressive robotic self-assembly," Living Machines Projects, MIT Artificial Intelligence Laboratory, 2002; http://www.ai.mit.edu/projects/living-machines/projects/self-assembly.shtml.

1279. Lijin Aryananda, "Multi-cellularity: origin, organization, and reproduction," Living Machines Projects, MIT Artificial Intelligence Laboratory, 2002; http://www.ai.mit.edu/projects/living-machines/projects/multi-cellularity.shtml.

1280. Martin C. Martin, "Eden," Living Machines Projects, MIT Artificial Intelligence Laboratory, 2002; http://www.ai.mit.edu/projects/living-machines/projects/eden.shtml; Martin C. Martin, "Complexity from a simple bag of tricks," MIT AI Lab Research Abstracts, September 2001; http://www.ai.mit.edu/projects/living-machines/publications/martin-martin-abstract2001.pdf.

1281. Gregory S. Chirikjian, "Kinematics of a metamorphic robotic system," Proc. 1994 IEEE Intl. Conf. On Robotics and Automation, San Diego, CA, May 1994, pp. 449-455; http://custer.me.jhu.edu/paper/knm_mtmfic/knm_mtmfic.html.

1282. Gregory S. Chirikjian, Amit Pamecha, Imme Ebert-Uphoff, "Evaluating efficiency of self-reconfiguration in a class of modular robots," J. Robotic Systems 13(1996):317-338; http://custer.me.jhu.edu/paper/evaluat/evaluat.html. See generally: http://custer.me.jhu.edu/.

1283. A. Pamecha, C. Chiang, D. Stein, G.S. Chirikjian, "Design and implementation of metamorphic robots," in J. McCarthy, ed., Proc. 1996 ASME Design Engineering Technical Conf. and Computers in Engineering Conf., ASME, 1996.

1284. Gregory S. Chirikjian, Jackrit Suthakorn, J. Zhou, "Self-replicating robot: A project in the mechatronics at Johns Hopkins University," JHU, Spring 2002; http://custer.me.jhu.edu/mechatronics/syllabus2002.htm.

1285. Gregory S. Chirikjian, Jackrit Suthakorn, "Toward self-replicating robots," Paper #067, Session 8: Design, 9 July 2002, Proc. 8th Intl. Symp. on Experimental Robotics (ISER '02), Italy, 8-11 July 2002; http://caesar.me.jhu.edu/jackritweb/iser2002.pdf or http://www.iser02.unisa.it/papers/67.pdf.

1286. Jackrit Suthakorn, "Self-Replicating Robots," http://caesar.me.jhu.edu/html/self_replicating_systems.html.

1287. Jackrit Suthakorn, "Part III: Self-Replicating Robots," in Paradigms of Service Robotics, Ph.D. Dissertation, Department of Mechanical Engineering, Johns Hopkins University, Baltimore, Maryland, February 2003, pp. 167-236; http://caesar.me.jhu.edu/jackritweb/Thesis011403.pdf.

1288. Jackrit Suthakorn, Y.T. Kwon, G.S. Chirikjian, "A semi-autonomous replicating robotic system," Proc. 2003 IEEE Intl. Symp. on Computational Intelligence in Robotics and Automation (CIRA), Kobe, Japan, 2003; http://caesar.me.jhu.edu/jackritweb/CIRA2003.pdf.

1289. Jackrit Suthakorn, Andrew B. Cushing, Gregory S. Chirikjian, "An autonomous self-replicating robotic system," Proc. 2003 IEEE/ASME Intl. Conf. on Advanced Intelligent Mechatronics (AIM 2003), Kobe, Japan, 2003; http://custer.me.jhu.edu/publication/pdf/auton.pdf or http://caesar.me.jhu.edu/jackritweb/AIM2003.pdf; IEEE/ASME Trans. Mechatronics (submitted December 2003).

1290. Jackrit Suthakorn et al, "The intelligence of an autonomous self-replicating robotic system," submitted for review, 2003.

1291. For example: Barry Brian Werger, "Scalable Behavior-Based Multi-Robot Systems," Interaction Lab, University of Southern California, 12 February 2001, http://robotics.usc.edu/~barry/proj-page.html; Gabe Sibley, "SCOWR (Scalable Coordination of Wireless Robots)," University of Southern California, 24 October 2001, http://www-robotics.usc.edu/projects/scowr/; Jens Wawerla, "Collective Construction with Multiple Robots," Robotics Research Labs, University of Southern California, 21 February 2002, http://www-robotics.usc.edu/projects/collectiveconstruction/; Brian P. Gerkey, "Auction-based Multi-Robot Coordination," University of Southern California, 13 February 2003, http://robotics.usc.edu/~gerkey/research/murdoch.html.

1292. "A Semi Replicating Robotic System (Summer 2002)," ~33 MB AVI video clip of Suthakorn-Chirikjian semi-self-replicating robots; http://caesar.me.jhu.edu/jackritweb/semisrr.avi.

1293. "An Autonomous Self-Replicating Robotic System (Fall 2002)," ~21 MB AVI video clip of Suthakorn-Chirikjian auto-self-replicating robots; http://caesar.me.jhu.edu/jackritweb/autosrr.avi.

1294. NASA Institute for Advanced Concepts (NIAC), http://www.niac.usra.edu/; Universities Space Research Association (USRA); http://www.usra.edu/.

1295. Hod Lipson, "Autonomous Self-Extending Machines for Accelerating Space Exploration," 1 May 2002 to 31 October 2002, NASA Institute for Advanced Concepts (NIAC); Abstract, http://www.niac.usra.edu/files/studies/abstract/737Lipson.html; Annual Meeting Presentation, http://www.niac.usra.edu/files/library/fellows_mtg/oct02_mtg/pdf/737Lipson.pdf.

1296. Hod Lipson, Evan Malone, "Autonomous Self-Extending Machines for Accelerating Space Exploration," NIAC CP 01-02, Advanced Aeronautical/Space Concept Studies Phase I Report, Final Report, 2002; http://www.niac.usra.edu/files/studies/final_report/pdf/737Lipson.pdf.

1297. Gregory Chirikjian, "Architecture for Unmanned Self-Replicating Lunar Factories," 1 October 2003 to 31 March 2004, NASA Institute for Advanced Concepts (NIAC); http://www.niac.usra.edu/files/studies/abstract/880Chirikjian.html; Gregory S. Chirikjian, "An Architecture for Self-Replicating Lunar Factories," NIAC Phase I Award: 1 October 2003 — 31 March 2004, Final Report, 26 April 2004; http://www.niac.usra.edu/files/studies/final_report/pdf/880Chirikjian.pdf.

1298. Paul Todd, “Robotic Lunar Ecopoiesis Test Bed,” 1 October 2003 to 31 March 2004, NASA Institute for Advanced Concepts (NIAC); http://www.niac.usra.edu/files/studies/abstract/884Todd.html.

1299. Tihamer Toth-Fejel, “Modeling Kinematic Cellular Automata: An Approach to Self-Replication,” 1 October 2003 to 31 March 2004, NASA Institute for Advanced Concepts (NIAC); http://www.niac.usra.edu/files/studies/abstract/883TothFejel.html; Tihamer Toth-Fejel, “Modeling Kinematic Cellular Automata: Final Report,” NASA Institute for Advanced Concepts, Phase I: CP-02-02, General Dynamics Advanced Information Systems Contract #P03-0984, 30 April 2004; http://www.niac.usra.edu/files/studies/final_report/pdf/883Toth-Fejel.pdf.

1300. “Robosphere: 2002 Workshop on Self Sustaining Robotic Ecologies,” NASA/Ames Research Center (Computational Sciences Division) and the Research Institute for Advanced Computer Science (RIACS), 14-15 November 2002; http://robosphere.arc.nasa.gov/Workshop2002.html.

1301. “Robosphere,” Computational Sciences Division, NASA/Ames Research Center, 2002; http://robosphere.arc.nasa.gov/index.html. See also: S. Colombano, Robosphere: Self-Sustaining Robotic Ecologies as Precursors to Human Planetary Exploration, AIAA 2003-6278, AIAA Space 2003 Conference & Exposition, Long Beach, California, USA, 23-25 September 2003, AIAA, Reston, Virginia, 2003.

1302. Evan Malone, Hod Lipson, “Solid free-form fabrication for self-sustained robot ecologies: Challenges and opportunities,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002, pp. 93-98.

1303. Sanjiv Singh, Reid Simmons, “Coordination of Robotic Teams for Assembly Operations,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002.

1304. Eric Matson, Scott A. DeLoach, “Organizational Model for Cooperative and Sustaining Robotic Ecologies,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002, pp. 5-9; http://www.cis.ksu.edu/~sdeloach/publications/Conference/Robosphere-Matson-DeLoach.pdf.

1305. Greg Pisanich, Larry Young, “An Aerobot Ecology,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002.

1306. Wei-Min Shen, Peter Will, “Self Reconfigurable Robots for Robosphere,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002.

1307. Terry Huntsberger, Hrand Aghazarian, Ashitey Trebi-Ollennu, Paul Schenker, “CAMPOUT: Behavior-Based Control for Autonomous Robotic Outposts,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002.

1308. Lorenzo Flückiger, Christian Neukom, Mike Wagner, Laura Plice, Cory Ippolito, Greg Pisanich, “A Facility And Architecture For Autonomy Research,” Proc. Robosphere 2002, Workshop on Self Sustaining Robotic Ecologies, NASA/Ames Research Center, CA, 14-15 November 2002.

1309. David Cohen, “Plasma blobs hint at new form of life,” NewScientist.com, 17 September 2003; http://www.newscientist.com/news/news.jsp?id=ns99994174.

1310. Erzilia Lozneanu, Mircea Sanduloviciu, “Minimal-cell system created in laboratory by self-organization,” Chaos, Solitons & Fractals 18(October 2003):335-343.

1311. Edmond Hamilton, Outside the Universe, 1929; Frank Belknap Long, “The Flame Midget,” 1935; Frank Belknap Long, “The Flame of Life,” 1939; Hal Clement, “Proof,” 1942; Eric Frank Russell, Sinister Barrier, 1943; Fred Hoyle, The Black Cloud, 1957; Arthur C. Clarke, “Out of the Sun,” 1958; Edmond Hamilton, Sunfire, 1962; Gregory Benford, Gordon Eklund, If the Stars Are Gods, 1977.

1312. Saul Griffith, “Self-replicating machines (mechanical morphogenesis),” communication to Robert A. Freitas Jr., 19 October 2003; password-protected research website: http://web.media.mit.edu/~saul/aaa/index.htm.

1313. Rex Stephens, “The Preparation,” 1999-2003; http://thepreparation.net. See also: “http://www.permanent.com” www.permanent.com.

1314. Valentí E. Pineda, personal communications to Robert A. Freitas Jr., on: 3, 9, 22, 23 July 2003; 7 August 2003; 2, 24 September 2003; 4 October 2003; 8, 15, 25 November 2003; and 9 December 2003. See also: Rex Stephens, “Self-Replicating Robotic Lunar Factory,” 1999-2003; http://thepreparation.net/SRRLF.html.

1315. Walter R. Stahl, Harry E. Goheen, “Molecular algorithms,” J. Theor. Biol. 5(1963):266-287.

1316. H.H. Pattee, “Physical theories, automata, and the origin of life,” in H.H. Pattee, E.A. Edelsack, Louis Fein, A.B. Callahan, eds., Natural Automata and Useful Simulations, Spartan Books, Washington, DC, 1966, pp. 73-105.

1317. Aristides A.G. Requicha, “Nanorobots, NEMS and nanoassembly,” Proc. IEEE, Special Issue on Nanoelectronics and Nanoprocessing (invited paper), 14-19 September 2003 ICRA International Conference on Robotics and Automation 2003, Taipei, Taiwan; http://www-lmr.usc.edu/~lmr/publications/RequichaProc2-25.pdf.

1318. Avery Dennison Microreplication, 2003, http://www.microreplication.com; Multi Media Replication Ltd., 2003, http://www.replication.com.

1319. J. Storrs Hall, “IMM Report: Reflexive capabilities,” IMM Report No. 7, Foresight Update 35, 30 January 1999, pp. 21-23; http://www.imm.org/Reports/Rep007.html.

1320. Pier Luigi Luisi, personal communication to Robert A. Freitas Jr., 30 September 2003.

1321. G.W. Whitesides, B. Grzybowski, “Self-assembly at all scales,” Science 295(29 March 2002):2418-2421; http://www.sciencemag.org/cgi/content/full/295/5564/2418.

1322. Richard D. Klafter, Thomas A. Chmielewski, Michael Negin, Robotic Engineering: An Integrated Approach, Prentice-Hall, NJ, 1989.

1323. G.R. Fleischaker, S. Colonna, P.L. Luisi, eds., Self-Production of Supramolecular Structures From Synthetic Structures to Models of Minimal Living Systems, NATA Asi Ser. C, Vol. 446, Kluwer Academic, Dordrecht, 1994.

1324. Leonard F. Lindoy, I.M. Atkinson, Self-Assembly in Supramolecular Systems, Royal Society of Chemistry, 2000; http://www.rsc.org/is/books/selfassembly.htm.

1325. W. Muller, H. Ringsdorf, E. Rump, G. Wildburg, X. Zhang, L. Angermaier, W. Knoll, M. Liley, J. Spinke, “Attempts to mimic docking processes of the immune system: recognition-induced formation of protein multilayers,” Science 262(10 December 1993):1706-1708.

1326. G.M. Whitesides, J.P. Mathias, C. Seto, “Molecular self-assembly and nanochemistry: A chemical strategy for the synthesis of nanostructures,” Science 254(1991):1312-1319. See also: G.M Whitesides, “Self-assembling materials,” Sci. Amer. 273(September 1995):146-149; George M. Whitesides, “Self assembly and nanotechnology,” Fourth Foresight Conference on Molecular Nanotechnology, 9-11 November 1995; http://www.zyvex.com/nanotech/nano4/whitesidesAbstract.html.

1327. Rudiger Berger, Emmanuel Delamarche, Hans Peter Lang, Christoph Gerber, James K. Gimzewski, Ernst Meyer, Hans-Joachim Guntherodt, “Surface stress in the self-assembly of alkanethiols on gold,” Science 276(27 June 1997):2021-2024.

1328. A. Ulman, An Introduction to Ultrathin Organic Films, From Langmuir-Blodgett to Self-Assembly, Academic Press, Boston, 1991.

1329. I.A. Aksay, M. Trau, S. Manne, I.I. Honma, N. Yao, L. Zhou, P. Fenter, P.M. Eisenberger, S.M. Gruner, “Biomimetic pathways for assembling inorganic thin films,” Science 273(16 August 1996):892-898.

1330. Rivka Maoz, Sophie Matlis, Elaine DiMasi, Benjamin M. Ocko, Jacob Sagiv, “Self-replicating amphiphilic monolayers,” Nature 384(14 November 1996):150-153.

1331. J.A. Zasadzinski, R. Viswanathan, L. Madsen, J. Garnaes, D.K. Schwartz, “Langmuir-Blodgett films,” Science 263(25 March 1994):1726-1733.

1332. P.A. Bachmann, P. Walde, P.L. Luisi, J. Lang, “Self-replicating micelle: aqueous micelles and enzymatically driven reactions in reverse micelles,” J. Am. Chem. Soc. 113(1991):8204-8209.

1333. P.A. Bachmann, P.L. Luisi, J. Lang, “Autocatalytic self-replicating micelles as models for prebiotic structures,” Nature 357(1992):57-59.

1334. Thomas Oberholzer, Roger Wick, Pier Luigi Luisi, Christof K. Biebricher, “Enzymatic RNA replication in self-reproducing vesicles: an approach to a minimal cell,” Biochem. Biophys. Res. Commun. 207(6 February 1995):250-257.

1335. Hiroshi Noguchi, Masako Takasu, “Self-assembly of amphiphiles into vesicles: A Brownian dynamics simulation,” Phys. Rev. E 64(2001):41913.

1336. Wiley P. Kirk, Mark A. Reed, eds., Nanostructures and Mesoscopic Systems, Academic Press, 1992.

1337. S.I. Stupp, V. LeBonheur, K. Walker, L.S. Li, K.E. Huggins, M. Keser, A. Amstutz, “Supramolecular materials: self-organized nanostructures,” Science 276(18 April 1997):384-389.

1338. Michael B. Cohn, “Method and apparatus for the assembly of microfabricated devices,” United States Patent No. 5,355,577, 18 October 1994; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,355,577.WKU.&OS=PN/5,355,577.

1339. M.B. Cohn, R.T. Howe, A.P. Pisano, “Self-assembly of microsystems using noncontact electrostatic traps,” ASME Intl. Congress and Exposition, Symposium on Micromechanical Systems, San Francisco, CA, 12-17 November 1995, pp. 893-900.

1340. K.-F. Bohringer, B.R. Donald, R. Mihailovich, N.C. Macdonald, “A theory of manipulation and control for microfabricated actuator arrays,” Proc. IEEE Workshop on Micro Electro Mechanical Systems (MEMS), January 1994, pp. 102-107.

1341. K. Bohringer, K. Goldberg, M. Cohn, R. Howe, A. Pisano, “Parallel microassembly with electrostatic force fields,” Proc. 1997 IEEE Intl. Conf. On Robotics and Automation, 1997.

1342. P.H. Moncevicz, M.J. Jakiela, K.T. Ulrich, “Orientation and insertion of randomly presented parts using vibratory agitation,” in A.H. Soni, ed., Proc. ASME Third Conf. On Flexible Assembly Systems, Amer. Soc. Mech. Eng., New York, Vol. DE-33, September 1991, pp. 41-47.

1343. K. Hosokawa, I. Shimoyama, H. Miura, “Two-dimensional micro-self-assembly using the surface tension of water,” IEEE J. Microelectromech. Syst. (1996).

1344. A. Terfort, G.M. Whitesides, “Self-assembly of an operating electrical circuit based on shape complementarity and the hydrophilic effect,” Adv. Mater. 10(1998):470-473.

1345. H.J. Yeh, J.S. Smith, “Fluidic self-assembly of GaAs microstructures on Si substrates,” Sens. Mater. 6(1994):319-332; H. Yeh, J.S. Smith, “Fluidic self-assembly for the integration of GaAs light-emitting diodes on Si substrates,” IEEE Photonics Technology Letters 6(June 1994):706-708.

1346. Uthara Srinivasan, Dorian Liepmann, Roger T. Howe, “Microstructure to substrate self-assembly using capillary forces,” J. Microelectromechanical Syst. 10(March 2001):17-24; http://www.me.berkeley.edu/~liepmann/assets/Thara-selfassembly.JMEMS.pdf.

1347. X. Xiong, Y. Hanein, W. Wang, D.T. Schwartz, K.F. Bohringer, “Controlled part-to-substrate micro-assembly via electrochemical modulation of surface energy,” Intl. Conf. on Solid-State Sensors and Actuators (Transducers’01), Munich, Germany, 2001; http://www.ee.washington.edu/faculty/karl/ Publications/TRANS01-xiaorong.pdf.

1348. X. Xiong, Y. Hanein, W. Wang, D.T. Schwartz, K.F. Bohringer, “Multi-batch micro-self-assembly via controlled capillary forces,” Intl. Conf. on Intelligent Robots and Systems (IEEE/RSJ IROS 2001), Maui, HI, 2001.

1349. K.F. Bohringer, U. Srinivasan, R.T. Howe, “Modeling of capillary forces and binding sites for fluidic self-assembly,” Intl. Conf. on Micro Electro Mechanical Systems (IEEE MEMS’01), Interlaken, Switzerland, 2001.

1350. X. Xiong, Y. Hanein, J. Fang, D.T. Schwartz, K.F. Bohringer, “Multi-batch self-assembly for microsystem integration,” 3rd Intl. Workshop on Microfactories (IWMF’02), Minneapolis, MN, 2002.

1351. Xiaorong Xiong, Yael Hanein, Jiandong Fang, Yanbing Wang, Weihua Wang, Daniel T. Schwartz, Karl F. Bohringer, “Controlled multi-batch self-assembly of micro devices,” UWEE Tech Report Series, UWEETR-2002-0006, 2002; https://www.ee.washington.edu/techsite/papers/documents/UWEETR-2002-0006.pdf.

1352. T.L. Breen, J. Tien, S.R.J. Oliver, T. Hadzic, G.M. Whitesides, “Design and self-assembly of open, regular, 3-D mesostructures,” Science 284(7 May 1999):948.

1353. N.B. Bowden, M. Weck, I.S. Choi, G.M. Whitesides, “Molecule-mimetic chemistry and mesoscale self-assembly,” Acc. Chem. Res. 34(2001):231-238.

1354. T.D. Clark, J. Tien, D.C. Duffy, K.E. Paul, G.M. Whitesides, “Self-assembly of 10-micron-sized objects into ordered three dimensional arrays,” J. Am. Chem. Soc. 123(2001):7677-7682.

1355. D.H. Gracias, V. Kavthekar, J.C. Love, K.E. Paul, G.M. Whitesides, “Fabrication of micrometer-scale, patterned polyhedra by self-assembly,” Adv. Mater. 14(5 February 2002):235-238.

1356. Jessamine M.K. Ng, Michael J. Fuerstman, Bartosz A. Grzybowski, Howard A. Stone, George M. Whitesides, “Self-assembly of gears at a fluid/air interface,” J. Am. Chem. Soc. 125(2003):7948-7958. See also: Philip Ball, “Gear change for miniature machines,” Nature ScienceUpdate, 16 June 2003; http://www.nature.com/nsu/030609/030609-17.html.

1357. Yu Huang, Xiangfeng Duan, Q. Wei, Charles M. Lieber, “Directed assembly of one-dimensional nanostructures into functional networks,” Science 291(26 January 2001):630-633; Z. Zhong, D. Wang, Y. Cui, M.W. Bockrath, C.M. Lieber, “Nanowire crossbar arrays as address decoders for integrated nanosystems,” Science 302(21 November 2003):1377-1379.

1358. Edward A. Rietman, Molecular Engineering of Nanosystems, AIP Series, Springer-Verlag, New York, 2001.

1359. Zhenli L. Zhang, Mark A. Horsch, Monica H. Lamm, Sharon C. Glotzer, “Tethered nano building blocks: toward a conceptual framework for nanoparticle self-assembly,” Nano Letters 3(October 2003):1341; http://www.engin.umich.edu/dept/che/research/glotzer/documents/2003TetheredNanoBuildingBlocks.pdf; Monica H. Lamm, T. Chen, Sharon C. Glotzer, “Simulated assembly of nanostructured organic/inorganic networks,” Nano Letters 3(August 2003):989; http://www.engin.umich.edu/dept/che/research/glotzer/documents/2003SimulatedAssemblyofNano.pdf; Mark Puls, “U-M researchers take giant leap toward fulfilling nanotech’s promise,” Michigan SmallTech, 1 December 2003; http://www.michigansmalltech.com/News/detail.asp?ContentId=2D89A976-EC08-4342-99CF-DA6E0970E5AC. See also: Steen Rasmussen, Donatella Pasqulini, “Multiscale simulation of molecular self-assembly,” Poster Presentation, Second Astrobiology Science Conference, NASA/AMES Research Center, 7-11 April 2002; http://www.astrobiology.com/asc2002/abstract.html?ascid=337 (abstract).

1360. Jean-Marie Lehn, Supramolecular Chemistry: Concepts and Perspectives, VCH, New York, 1995.

1361. D. Sievers, G. von Kiedrowski, “Self-replication of complementary nucleotide-based oligomers,” Nature 369(19 May 1994):221-224, 184-185 (comment).

1362. A. Luther, R. Brandsch, G. von Kiedrowski, “Surface-promoted replication and exponential amplification of DNA analogues,” Nature 396(19 November 1998):245-248.

1363. M. Scheffler, A. Dorenbeck, S. Jordan, M. Wustefeld, G. von Kiedrowski, “Self-assembly of trisoligonucleotidyls: the case for nano-acetylene and nano-cyclobutadiene,” Angew. Chem. Int. Ed. Engl. 38(1999):3311-3315.

1364. G. von Kiedrowski, “Molekulare Prinzipien der artifiziellen Selbstreplikation,” in D. Ganten, ed., Gene, Nerone, Qubits & Co. Unsere Welten der Information, S. Hirzel Verlag, Stuttgart, Germany, 1999, pp. 123-145.

1365. G. von Kiedrowski, B. Wlotzka, J. Helbling, J. Angew. Chem. 101(1989):1259-1261.

1366. G. von Kiedrowski, B. Wiotzka, J. Hielbing, M. Matzan, S. Jordan, Angew. Chem. Int. Ed. Engl. 30(1991):423-426.

1367. T. Achilles, G. von Kiedrowski, “A self-replicating system from three starting materials,” Angew. Chem. Int. Ed. Engl. 32(1993):1198-1201.

1368. J.S. Griffith, “Self-replication and scrapie,” Nature 215(2 September 1967):1043-1044.

1369. M. Famulok, J.S. Nowick, J. Rebek, Jr., “Self-replicating systems,” Acta Chem. Scand. 46(1992):315-324.

1370. L.E. Orgel, “Molecular replication,” Nature 358(16 July 1992):203-209.

1371. J. Maddox, “Towards synthetic self-replication,” Nature 354(5 December 1991):351.

1372. Natasha Paul, Gerald F. Joyce, “A self-replicating ligase ribozyme,” Proc. Natl. Acad. Sci. (USA) 99(1 October 2002):12733-12740; http://www.pnas.org/cgi/content/full/99/20/12733.

1373. G. von Kiedrowski, “A self-replicating hexadeoxynucleotide,” Angew. Chem. Int. Ed. Engl. 25(1986):932-935.

1374. A. Robertson, A.J. Sinclair, D. Philp, “Minimal self-replicating systems,” Chem. Soc. Rev. 29(March 2000):141-152; http://www.rsc.org/CFmuscat/intermediate.cfm?FURL=/ej/CS/2000/a803602k.PDF.

1375. W.S. Zielinski, L.E. Orgel, “Autocatalytic synthesis of a tetranucleotide analogue,” Nature 327(28 May - 3 June 1987):346-347.

1376. B.G. Bag, G. von Kiedrowski, “Templates, autocatalysis and molecular replication,” Pure Appl. Chem. 68(November 1996):2145-2152.

1377. R. Naylor, P.T. Gilham, “Studies on some interactions and reactions of oligonucleotides in aqueous solution,” Biochemistry 5(August 1966):2722-2728.

1378. R. Lohrmann, L.E. Orgel, "Self-condensation of activated dinucleotides on polynucleotide templates with alternating sequences," J. Mol. Evol. 14(December 1979):243-250; R. Lohrmann, L.E. Orgel, "Studies of oligoadenylate formation on a poly (U) template," J. Mol. Evol. 12(15 March 1979):237-257; J. Ninio, L.E. Orgel, "Heteropolynucleotides as templates for non-enzymatic polymerizations," J. Mol. Evol. 12(29 December 1978):91-99.
1379. T. Inoue, L.E. Orgel, "A nonenzymatic RNA polymerase model," Science 219(18 February 1983):859-862.
1380. R. Rohatgi, D.P. Bartel, J.W. Szostak, "Kinetic and mechanistic analysis of nonenzymatic, template-directed oligoribonucleotide ligation," J. Am. Chem. Soc. 118(10 April 1996):3332-3339.
1381. Z.Y.J. Zhan, D.G. Lynn, "Chemical amplification through template-directed synthesis," J. Am. Chem. Soc. 119(17 December 1997):12420-12421.
1382. D.H. Lee, K. Severin, M.R. Ghadiri, "Autocatalytic networks: the transition from molecular self-replication to molecular ecosystems," Curr. Opin. Chem. Biol. 1(December 1997):491-496.
1383. D.H. Lee, K. Severin, M.R. Ghadiri, "Dynamic error correction in autocatalytic peptide networks," Angew. Chem. Int. Ed. Engl. 37(1998):126-128.
1384. D.H. Lee, K. Severin, Y. Yokobayashi, M.R. Ghadiri, "Emergence of symbiosis in peptide self-replication through a hypercyclic network," Nature 390(11 December 1997):591-594; Nature 394(2 July 1998):101 (erratum).
1385. D.H. Lee, J.R. Granja, J.A. Martinez, K. Severin, M.R. Ghadiri, "A self-replicating peptide," Nature 382(8 August 1996):525-528. See also: K. Severin, D.H. Lee, J.A. Martinez, M.R. Ghadiri, "Peptide self-replication via template-directed ligation," Chemistry-A European J. 3(1997):1017-1024.
1386. Shao Yao, Indraneel Ghosh, Reena Zutshi, Jean Chmielewski, "A pH-modulated, self-replicating peptide," J. Am. Chem. Soc. 119(29 October 1997):10559-10560; http://www.haverford.edu/biology/Courses/Bio303/design_papers/design5.pdf. See also: S. Yao, I. Ghosh, R. Zutshi, J. Chmielewski, "Selective amplification by auto- and crosscatalysis in a replicating peptide system," Nature 396(1998):447-450.
1387. R. Issac, J. Chmielewski, "Approaching exponential growth with a self-replicating peptide," J. Am. Chem. Soc. 124(19 June 2002):6808-6809. See also: R. Issac, Y.W. Ham, J. Chmielewski, "The design of self-replicating helical peptides," Curr. Opin. Struct. Biol. 11(August 2001):458-463; X. Li, J. Chmielewski, "Challenges in the design of self replicating peptides," Org. Biomol. Chem. 1(21 March 2003):901-904.
1388. C. Bohler, P.E. Nielsen, L.E. Orgel, "Template switching between PNA and RNA oligonucleotides," Nature 376(17 August 1995):578-581, 548-549 (comment).
1389. M. Koppitz, P.E. Nielsen, L.E. Orgel, "Formation of oligonucleotide-PNA-chimeras by template-directed ligation," J. Am. Chem. Soc. 120(1998):4563-4569.
1390. J.G. Schmidt, L. Christensen, P.E. Nielsen, L.E. Orgel, "Information transfer from DNA to peptide nucleic acids by template-directed syntheses," Nucleic Acids Res. 25(1 December 1997):4792-4796; http://nar.oupjournals.org/cgi/content/full/25/23/4792. J.G. Schmidt, P.E. Nielsen, L.E. Orgel, "Information transfer from peptide nucleic acids to RNA by template-directed syntheses," Nucleic Acids Res. 25(1 December 1997):4797-4802; http://nar.oupjournals.org/cgi/content/full/25/23/4797.
1391. M. Levy, A.D. Ellington, "Peptide-templated nucleic acid ligation," J. Mol. Evol. 56(May 2003):607-615.
1392. S. Matsumura, T. Takahashi, A. Ueno, H. Mihara, "Complementary nucleobase interaction enhances peptide-peptide recognition and self-replicating catalysis," Chemistry 9(6 October 2003):4829-4837.
1393. M.R. Ghadiri, J.R. Granja, R.A. Milligan, D.E. McRee, N. Khazanovich, "Self-assembling organic nanotubes based on a cyclic peptide architecture," Nature 366(25 November 1993):324-327.
1394. T.D. Clark, M.R. Ghadiri, "Supramolecular design by covalent capture: design of a peptide cylinder via hydrogen bond-promoted intermolecular olefin metathesis," J. Am. Chem. Soc. 117(1995):12364-12365.
1395. J.M. Buriak, M.R. Ghadiri, "Self-assembly of peptide based nanotubes," Mater. Sci. Eng. C4(1997):207-212.
1396. H.S. Kim, J.D. Hartgerink, M. Reza Ghadiri, "Oriented self-assembly of cyclic peptide nanotubes in lipid membranes," J. Am. Chem. Soc. 120(1998):4417-4424.
1397. Thomas D. Clark, Lukas K. Buehler, M. Reza Ghadiri, "Self-assembling cyclic beta-3-peptide nanotubes as artificial transmembrane ion channels," J. Am. Chem. Soc. 120(1998):651-656.
1398. D.T. Bong, T.D. Clark, J.R. Granja, M.R. Ghadiri, "Self-assembling organic nanotubes," Angew. Chem. Int. Ed. Engl. 40(16 March 2001):988-1011.
1399. K. Kobayashi, J.R. Granja, M.R. Ghadiri, "Beta-sheet peptide architecture: measuring the relative stability of parallel vs. antiparallel beta-sheets," Angew. Chem. Int. Ed. Engl. 34(1995):95-98.
1400. N. Khazanovich, J.R. Granja, D.E. McRee, R.A. Milligan, M.R. Ghadiri, "Nanoscale tubular ensembles with specified internal diameters: design of a self-assembled nanotube with a 13-Angstrom pore," J. Am. Chem. Soc. 116(1994):6011-6012.
1401. M. Reza Ghadiri, Juan R. Granja, Lukas K. Buehler, "Artificial transmembrane ion channels from self-assembling peptide nanotubes," Nature 369(26 May 1994):301-304; 276-277 (comment).
1402. J.R. Granja, M.R. Ghadiri, "Channel-mediated transport of glucose across lipid bilayers," J. Am. Chem. Soc. 116(1994):10785-10786.
1403. Th. Zemb, M. Dubois, B. Deme, Th. Gulik-Krzywicki, "Self-assembly of flat nanodiscs in salt-free catanionic surfactant solutions," Science 283(5 February 1999):816-819.
1404. Steve Santoso, Wonmuk Hwang, Hyman Hartman, Shuguang Zhang, "Self-assembly of surfactant-like peptides with variable glycine tails to form nanotubes and nanovesicles," Nano Letters 2(July 2002):687-691; http://cba.mit.edu/publications/02.07.santoso.pdf. See also: Sylvain Vauthey, Steve Santoso, Haiyan Gong, Nicki Watson, Shuguang Zhang, "Molecular self-assembly of surfactant-like peptides to form nanotubes and nanovesicles," Proc. Natl. Acad. Sci. (USA) 99(2002):5355-5360; http://www.pnas.org/cgi/content/full/99/8/5355.
1405. Shuguang Zhang, Davide M. Marini, Wonmuk Hwang, Steve Santoso, "Design of nanostructured biological materials through self-assembly of peptides and proteins," Curr. Opin. Chem. Biol. 6(2002):865-871; http://cba.mit.edu/publications/02.00.zhang.pdf.
1406. Céline Valéry, Maïté Paternostre, Bruno Robert, Thaddée Gulik-Krzywicki, Theyencheri Narayanan, Jean-Claude Dedieu, Gérard Keller, Maria-Luisa Torres, Roland Cherif-Cheikh, Pilar Calvo, Franck Artzner, "Biomimetic organization: Octapeptide self-assembly into nanotubes of viral capsid-like dimension," Proc. Natl. Acad. Sci. (USA) 100(2003):10258-10262; http://www.pnas.org/cgi/content/full/100/18/10258.
1407. Takashi Yokoyama, Shiyoshi Yokoyama, Toshiya Kamikado, Yoshishige Okuno, Shinro Mashiko, "Selective assembly on a surface of supramolecular aggregates with controlled size and shape," Nature 413(11 October 2001):619-621.
1408. Maxwell J. Crossley, University of Sydney, Australia; http://www.chem.usyd.edu.au/~crossley/.
1409. Pall Thordarson, Annie Marquis, Maxwell J. Crossley, "The synthesis and studies towards the self-replication of bis(capped porphyrins)," Org. Biomol. Chem. 1(2003):1216-1225. See also: Pall Thordarson, "Molecular Recognition of Bis-porphyrins: Towards Self-replication and Templated Synthesis," Ph.D. Dissertation, School of Chemistry, University of Sydney, Australia 2000.
1410. H. Fenniri, P. Mathivanan, K.A. Vidale, D.M. Sherman, K. Hallenga, K.V. Wood, J.G. Stowell, "Helical rosette nanotubes: design, self-assembly, and characterization," J. Am. Chem. Soc. 123(2001):3854-3855.
1411. Hicham Fenniri, Bo-Liang Deng, Jesus G. Moralez, Kathryn M. Gorman, Karen Jemio-Bedregal, "Self-assembled rosette nanotubes with predefined chemical and physical properties," paper presented at the 10th Foresight Conference on Molecular Nanotechnology, October 2002; http://www.foresight.org/Conferences/MNT10/Abstracts/Fenniri/index.html (abstract).
1412. Hicham Fenniri, Bo-Liang Deng, Alexander E. Ribbe, Klaas Hallenga, Jaby Jacob, Pappannan Thiyagarajan, "Entropically driven self-assembly of multichannel rosette nanotubes," Proc. Natl. Acad. Sci. (USA) 99(2002):6487-6492; http://www.chem.purdue.edu/hf/PNASpaper.pdf and http://www.pnas.org/papbyrecent.shtml.
1413. Hicham Fenniri, Bo-Liang Deng, Alexander E. Ribbe, "Helical rosette nanotubes with tunable chiroptical properties," J. Am. Chem. Soc. 124(2002):11064-11072; http://www.chem.purdue.edu/hf/Fenniri-JACS-082402.pdf.

1414. M.S. Shchepinov, K.U. Mir, J.K. Elder, M.D. Frank-Kamenetskii, E.M. Southern, “Oligonucleotide dendrimers: stable nano-structures,” Nucleic Acids Res. 27(1 August 1999):3035-3041, http://nar.oupjournals.org/cgi/content/full/27/15/3035; T.W. Nilsen, J. Grayzel, W. Prensky, “Dendritic nucleic acid structures,” J. Theor. Biol. 187(21 July 1997):273-284.

1415. T. Horn, M.S. Urdea, “Forks and combs and DNA: The synthesis of branched oligodeoxyribonucleotides,” Nucleic Acid Res. 17(12 September 1989):6959-6967.

1416. Christof M. Niemeyer, “DNA as a material for nanotechnology,” Angew. Chem. Int. Ed. Engl. 36(1997):585-587.

1417. Steven S. Smith, Luming Niu, David J. Baker, John A. Wendel, Susan E. Kane, Darrin S. Joy, “Nucleoprotein-based nanoscale assembly,” Proc. Natl. Acad. Sci. 94(18 March 1997):2162-2167; http://www.pnas.org/cgi/content/full/94/6/2162.

1418. Masad J. Damha, Kanjana Ganeshan, Robert H.E. Hudson, Steven V. Zabarylo, “Solid-phase synthesis of branched oligoribonucleotides related to messenger RNA splicing intermediates,” Nucleic Acid Res. 20(December 1992):6565-6573.

1419. Paul A. Giannaris, Masad J. Damha, “Oligoribonucleotides containing 2’-5’-phosphodiester linkages exhibit binding selectivity for 3’-5’-RNA over 3’-5’-ssDNA,” Nucleic Acid Res. 21(October 1993):4742-4749.

1420. R.H.E. Hudson, M.J. Damha, “Nucleic acid dendrimers — novel biopolymer structures,” J. Am. Chem. Soc. 115(24 March 1993):2119-2124.

1421. A.H. Uddin, M.A. Roman, J. Anderson, M.J. Damha, “A novel N3-functionalized thymidine linker for the stabilization of triple helical DNA,” Chem. Commun. (1996):171-172.

1422. T.C. Marsh, E.R. Henderson, “G-wires: Self-assembly of a telomeric oligonucleotide, d(GGGGTTGGGG), into large superstructures,” Biochemistry 33(6 September 1994):10718-10724.

1423. T.C. Marsh, J. Vesenka, E.R. Henderson, “A new DNA nanostructure, the G-wire, imaged by scanning probe microscopy,” Nucl. Acids Res. 23(25 February 1995):696-700.

1424. J. Vesekna, T. Marsh, R. Miller, E. Henderson, “Atomic force microscopy reconstruction of G-wire DNA,” J. Vac. Sci. Technol. B 14(1996):1413-1417.

1425. James Vesenka, Eric Henderson, Thomas Marsh, “Construction and examination of ‘G-wire’ DNA,” DNA-Based Molecular Construction: International Workshop on DNA-Based Molecular Construction, Jena, Germany, 23-25 May 2002; AIP Conference Proceedings, Vol. 640.1, 12 November 2002, pp. 99-109; http://content.aip.org/APCPCS/v640/i1/99_1.html.

1426. Lars Henning Eckardt, Kai Naumann, Wolf Matthias Pankau, Günter von Kiedrowski, “Nanorobots — From Fiction to Science,” paper O-47, XIIth Intl. Symp. on Supramolecular Chemistry, Eilat, Israel, 6-11 October 2002; http://chemsg7.tau.ac.il/~issc/Abs1/Kiedrowski.pdf.

1427. A. Dorenbeck, M. Scheffler, M. Wüstefeld, G. von Kiedrowski, “Noncovalent synthesis of a tetrahedral nanoscaffold from 3’-trisoligonucleotidyls with individually defined sequences,” Angew. Chem. Int. Ed. Engl., 2003, in press.

1428. Guenter von Kiedrowski, Lars-Henning Eckardt, Kai Naumann, Wolf Matthias Pankau, Malte Reimold, Michael Rein, “Toward replicatable, multifunctional, nanoscaffolded machines. A chemical manifesto,” Pure Appl. Chem. 75(2003):609-619.

1429. Lars Henning Eckardt, Kai Naumann, Wolf Matthias Pankau, Michael Rein, Markus Schweitzer, Norbert Windhab, Günter von Kiedrowski, “DNA nanotechnology: Chemical copying of connectivity,” Nature 420(21 November 2002):286; http://www.nature.com/nlink/v420/n6913/abs/420286a_fs.html.

1430. B.G. Bag, G. von Kiedrowski, “Stepwise Replication of a Troger’s Base Analogue,” Angew. Chem. Int. Ed. Engl. 38(16 December 1999):3713-3714.

1431. D. Liu, S.H. Park, J.H. Reif, T.H. LaBean, “DNA nanotubes self-assembled from triple-crossover tiles as templates for conductive nanowires,” Proc. Natl. Acad. Sci. (USA) 101(20 January 2004):717-722; http://www.pnas.org/cgi/content/full/101/3/717.

1432. T.W. Nilsen, J. Grayzel, W. Prensky, “Dendritic nucleic acid structures,” J. Theor. Biol. 187(21 July 1997):273-284.

1433. Y. Li, Y.D. Tseng, S.Y. Kwon, L. D’Espaux, J.S. Bunch, P.L. McEuen, D. Luo, “Controlled assembly of dendrimer-like DNA,” Nat. Mater. 3(January 2004):38-42.

1434. H. Yan, X. Zhang, Z. Shen, N.C. Seeman, “A robust DNA mechanical device controlled by hybridization topology,” Nature 415(3 January 2002):62-65.

1435. N.C. Seeman, A.M. Belcher, “Emulating biology: building nanostructures from the bottom up,” Proc. Natl. Acad. Sci. (USA) 99(30 April 2002):6451-6455 (Suppl 2); http://www.pnas.org/cgi/content/full/99/suppl_2/6451.

1436. Chengde Mao, Weiqiong Sun, Zhiyon Shen, Nadrian C. Seeman, “A nanomechanical device based on the B-Z transition of DNA,” Nature 397(14 January 1999):144-146.

1437. Erik Winfree, Furong Liu, Lisa A. Wenzler, Nadrian C. Seeman, “Design and self-assembly of two-dimensional DNA crystals,” Nature 394(6 August 1998):539-544; http://www.dna.caltech.edu/Papers/lattice.pdf or http://www.nature.com/server-java/Propub/nature/v394n6693.

1438. N.C. Seeman, “Nucleic acid junctions: Building blocks for genetic engineering in three dimensions,” in R.H. Sarma, ed., Biomolecular Stereodynamics, Adenine Press, New York, 1981, pp. 269-277.

1439. Nadrian C. Seeman et al., “New Motifs in DNA Nanotechnology,” Nanotechnology 9(September 1998):257-273.

1440. Junghuei Chen, Nadrian C. Seeman, “Synthesis from DNA of a molecule with the connectivity of a cube,” Nature 350(18 April 1991):631-633.

1441. C. Mao, T.H. LaBean, J.H. Relf, N.C. Seeman, “Logical computation using algorithmic self-assembly of DNA triple-crossover molecules,” Nature 407(28 September 2000):493-496.

1442. A. Carbone, N.C. Seeman, “Circuits and programmable self-assembling DNA structures,” Proc. Natl. Acad. Sci. (USA) 99(1 October 2002):12577-12582; http://www.pnas.org/cgi/content/full/99/20/12577.

1443. Yuwen Zhang, Nadrian C. Seeman, “Construction of a DNA-Truncated Octahedron,” J. Am. Chem. Soc. 116(1994):1661-1669.

1444. Nadrian C. Seeman et al., “New Motifs in DNA Nanotechnology,” Nanotechnology 9(September 1998):257-273.

1445. N.C. Seeman, “DNA in a material world,” Nature 421(23 January 2003):427-431.

1446. T.H. LaBean, H. Yan, J. Kopatsch, F. Liu, E. Winfree, J.H. Reif, N.C. Seeman, “The construction, analysis, ligation and self-assembly of DNA triple crossover complexes,” J. Am. Chem. Soc. 122(2000):1848-1860; http://www.cs.duke.edu/~reif/paper/DNAtiling/tilings/JACS.pdf or http://www.dna.caltech.edu/Papers/triplex.pdf.

1447. N.C. Seeman, “DNA nanotechnology: Novel DNA constructions,” Annu. Rev. Biophys. Biomol. Struct. 27(1998):225-248.

1448. Ned Seeman’s Laboratory Home Page; http://seemanlab4.chem.nyu.edu/homepage.html.

1449. N.C. Seeman, “At the crossroads of chemistry, biology, and materials: structural DNA nanotechnology,” Chem. Biol. 10(December 2003):1151-1159.

1450. N.C. Seeman, “Construction of three-dimensional stick figures from branched DNA,” DNA Cell Biol. 10(September 1991):475-486.

1451. C.M. Niemeyer, T. Sano, C.L. Smith, C.R. Cantor, “Oligonucleotide-directed self-assembly of proteins: semisynthetic DNA — streptavidin hybrid molecules as connectors for the generation of macroscopic arrays and the construction of supramolecular bioconjugates,” Nucleic Acids Res. 22(25 December 1994):5530-5539.

1452. John A. Wendel, Steven S. Smith, “Uracil as an alternative to 5-fluorocytosine in addressable protein targeting,” Nanotechnology 9(September 1998):297-304.

1453. C.M. Niemeyer, B. Ceyhan, S. Gao, L. Chi, S. Peschel, U. Simon, “Site-Selective Immobilization of Gold Nanoparticles Functionalized with DNA Oligomers,” Colloid Polym. Sci. 279(2001):68-72.

1454. C.M. Niemeyer, B. Ceyhan, “DNA-directed functionalization of colloidal gold with proteins,” Angew. Chem. Int. Ed. 40(2001):3685-3688.

1455. C.M. Niemeyer, J. Koehler, C. Wuerdemann, “DNA-directed assembly of bienzymic complexes from in-vivo biotinylated NAD(P)H:FMN oxidoreductase and luciferase,” Chem. BioChem. 3(2002):242-245.

1456. Steven S. Smith, “Designs for the self-assembly of open and closed macromolecular structures and a molecular switch using DNA methyltransferases to order proteins on nucleic acid scaffolds,” Nanotechnology 13(June 2002):413-419.

1457. Steven S. Smith, “Nucleoprotein assemblies,” in H.S. Nalwa, ed., Encyclopedia of Nanoscience and Nanotechnology, Vol. X, American Scientific Publishers, 2003, pp. 1-10.

1458. N.C. Seeman, “Nucleic acid junctions and lattices,” J. Theor. Biol. 99(1982):237-247.

1459. M.E.A. Churchill, T.D. Tullius, N.R. Kallenbach, N.C. Seeman, "A Holliday Recombination Intermediate is Twofold Symmetric," Proc. Natl. Acad. Sci. USA 85(1988):4653-4656. See also: M. Susman, B. Engels, "Strand Exchange and Translation of Holliday Junction," 27 July 1997; http://www.wisc.edu/genetics/Holliday/holliday3D.html.

1460. P.J. Hagerman, "Flexibility of DNA," Ann. Rev. Biophys. Biophys. Chem. 17(1988):265-286.

1461. N.C. Seeman, J.M. Rosenberg, A. Rich, "Sequence specific recognition of double helical nucleic acids by proteins," Proc. Natl. Acad. Sci. USA 73(1976):804-808.

1462. J.H. Chen, N.R. Kallenbach, N.C. Seeman, "A specific quadrilateral synthesized from DNA branched junctions," J. Am. Chem. Soc. 111(1989):6402-6407.

1463. Y. Zhang, N.C. Seeman, "A solid-support methodology for the construction of geometrical objects from DNA," J. Am. Chem. Soc. 114(1992):2656-2663.

1464. T.J. Fu, N.C. Seeman, "DNA double crossover structures," Biochemistry 32(1993):3211-3220.

1465. X. Li, X. Yang, J. Qi, N.C. Seeman, "Antiparallel DNA double crossover molecules as components for nanoconstruction," J. Am. Chem. Soc. 118(1996):6131-6140.

1466. W.M. Shih, J.D. Quispe, G.F. Joyce, "A 1.7-kilobase single-stranded DNA that folds into a nanoscale octahedron," Nature 427(12 February 2004):618-621; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14961116&dopt=Abstract.

1467. Liz Kalaugher, "DNA folds into nano-octahedra," NanoTechWeb, 11 February 2004; http://www.nanotechweb.org/articles/news/3/2/5/1.

1468. D.D. MacNicol, J.J. McKendrick, D.R. Wilson, "Clathrates and molecular inclusion phenomena," Chem. Soc. Rev. 7(1978):65-87.

1469. M. Simard, S. Dan, J.D. Wuest, "Use of hydrogen bonds to control molecular aggregation. Self-assembly of three-dimensional networks with large chambers," J. Am. Chem. Soc. 113(1991):4696-4698.

1470. Markus Krummenacker, "Steps towards molecular manufacturing," Chem. Design Autom. News 9(January 1994):1, 29-39; see also: http://www.ai.sri.com/~kr/nano/cda-news/cda-news.html.

1471. H. van Bekkum, E.M. Flanigen, J.C. Jansen, eds., Introduction to Zeolite Science and Practice, Elsevier, Amsterdam, 1991. See also: W.M. Meier, D.H. Olson, C. Baerlocher, Atlas of Zeolite Structure Types, Elsevier, Boston MA, 1996.

1472. George T. Kerr, "Synthetic zeolites," Sci. Amer. 261(July 1989):100-105. See also: John Meurig Thomas, "Solid acid catalysts," Sci. Amer. 266(April 1992):112-118.

1473. N. Herron, "Catalytic aspects of inclusion in zeolites," in J.L. Atwood, J.E.D. Davies, D.D. MacNicol, Inclusion Compounds, Vol. 5, Oxford University Press, Cambridge, 1991.

1474. Robert Pool, "The smallest chemical plants," Science 263(25 March 1994):1698-1699.

1475. D.W. Lewis, C.M. Freeman, C.R.A. Catlow, "Predicting the templating ability of organic additives for the synthesis of microporous materials," J. Phys. Chem. 99(1995):11194-11202.

1476. Mark E. Davis, "Design for sieving," Nature 382(15 August 1996):583-584.

1477. Victoria A. Russell, Cara C. Evans, Wenjie Li, Michael D. Ward, "Nanoporous molecular sandwiches: pillared two-dimensional hydrogen-bonded networks with adjustable porosity," Science 276(25 April 1997):575-579. See also: Steven C. Zimmerman, "Putting molecules behind bars," Science 276(25 April 1997):543-544.

1478. Wuzong Zhou, J.M. Thomas, D.S. Shephard, B.F.G. Johnson, D. Ozkaya, T. Maschmeyer, R.G. Bell, Q. Ge, "Ordering of ruthenium cluster carbonyls in mesoporous silica," Science 280(1 May 1998):705-708.

1479. Seong Su Kim, Wenzhong Zhang, Thomas J. Pinnavaia, "Ultrastable mesostructured silica vesicles," Science 282(13 November 1998):1302-1305.

1480. P.J. Fagan, M.D. Ward, J.C. Calabrese, "Molecular engineering of solid-state materials: Organometallic building blocks," J. Am. Chem. Soc. 111(1989):1698-1719.

1481. Stuart R. Batten, Bernard F. Hoskins, Richard Robson, "Two interpenetrating 3-D networks…," J. Am. Chem. Soc. 117(17 May 1995):5385-5386.

1482. D.T. Bong, M.R. Ghadiri, "Self-assembling cyclic peptide cylinders as nuclei for crystal engineering," Angew. Chem. Int. Ed. Engl. 40(1 June 2001):2163-2166.

1483. M.J. Zaworotko, "Crystal engineering of diamondoid networks," Chem. Soc. Rev. 23(1994):283-288.

1484. Alfons van Blaaderen, Rene Ruel, Pierre Wiltzius, "Template-directed colloidal crystallization," Nature 385(23 January 1997):321-324.

1485. X. Bu, P. Feng, G.D. Stucky, "Large-cage zeolite structures with multidimensional 12-ring channels," Science 278(19 December 1997):2080-2085.

1486. Stephen S.-Y. Chui, Samuel M.-F. Lo, Jonathan P.H. Charmant, A. Guy Orpen, Ian D. Williams, "A chemically functionalizable nanoporous material $[Cu_3(TMA)_2(H_2O)_3]_n$," Science 283(19 February 1999):1148-1150.

1487. Brian Korgel, Donald Fitzmaurice, "Self-assembly of silver nanocrystals into two-dimensional nanowire arrays," Advanced Materials 10(1998):610 (cover).

1488. Peidong Yang, Tao Deng, Dongyuan Zhao, Pingyun Feng, David Pine, Bradley F. Chmelka, George M. Whitesides, Galen D. Stucky, "Hierarchically ordered oxides," Science 282(18 December 1998):2244-2246.

1489. Franz X. Redl, Kyung Sang Cho, Christopher B. Murray, Stephen O'Brien, "Three-dimensional binary superlattices of magnetic nanocrystals and semiconductor quantum dots," Nature 423(26 June 2003):968-971, http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v423/n6943/abs/nature01702_fs.html (abstract); "Scientists Announce First 3-D Assembly of Magnetic and Semiconducting Nanoparticles," NSF Press Release NSF PR 03-68, 25 June 2003; http://www.nsf.gov/od/lpa/news/03/pr0368.htm. See images and animations at http://domino.research.ibm.com/Comm/bios.nsf/pages/selfassembly.html.

1490. Leslie A. Bursill, Laure N. Bourgeois, "Polyhedral nano-clusters with the potential for self-replication," Mod. Phys. Lett. B 13(30 April 1999):271-274.

1491. Z. Xu, J.S. Moore, "Synthesis and characterization of a high molecular weight stiff dendrimer," Angew. Chem. 105(1993):261; Angew. Chem. Int. Ed. Engl. 32(1993):246-248.

1492. Z. Xu, J.S. Moore, "Rapid construction of large-size phenylacetylene dendrimers up to 12.5 nanometers in molecular diameter," Angew. Chem. 105(1993):1394; Angew. Chem. Int. Ed. Engl. 32(1993):1354-1357.

1493. Z. Xu, B. Kyan, J.S. Moore, "Stiff dendritic macromolecules based on phenylacetylenes," in G.R. Newkome, ed., Advances in Dendritic Macromolecules, Volume 1, JAI Press, Greenwich CT, 1994, pp. 69-104.

1494. Donald A. Tomalia, "Dendrimer molecules," Sci. Amer. 272(May 1995):62-66.

1495. T. Kawaguchi, K.L. Walker, C.L. Wilkins, J.S. Moore, "Double exponential dendrimer growth," J. Am. Chem. Soc. 117(1995):2159-2165.

1496. C. Devadoss, P. Bharathi, J.S. Moore, "Energy transfer in dendritic macromolecules: Molecular size effects and the role of an energy gradient," J. Am. Chem. Soc. 118(1996):9635-9644.

1497. D.J. Pesak, J.S. Moore, T.E. Wheat, "Synthesis and characterization of water-soluble dendritic macromolecules with a stiff hydrocarbon interior," Macromolecules 30(1997):6467-6482.

1498. M.R. Shortreed, S.F. Swallen, Z.-Y. Shi, W. Tan, Z. Xu, C. Devadoss, J.S. Moore, R. Kopelman, "Directed energy transfer funnels in dendrimeric antenna supermolecules," J. Phys. Chem. 101(1997):6318-6322.

1499. O.A. Matthews, A.N. Shipway, J.F. Stoddart, "Dendrimers — branching out from curiosities into new technologies," Prog. Poly. Sci. 23(1998):1-56.

1500. Steven C. Zimmerman, Fanwen Zeng, "Dendrimers in supramolecular chemistry: From molecular recognition to self-assembly," Chem. Rev. 97(1997):1681-1712. See also: Steven C. Zimmerman, Fanwen Zeng, David E.C. Reichert, Sergei V. Kolotuchin, "Self-assembling dendrimers," Science 271(23 February 1996):1095-1098; Thomas W. Bell, "Molecular trees: A new branch of chemistry," Science 271(23 February 1996):1077-1078.

1501. George R. Newkome, Claus D. Weis, Charles N. Moorefield, Ingrid Weis, "Detection and functionalization of dendrimers possessing free carboxylic acid moieties," Macromolecules 30(1997):2300-2304.

1502. Jean Haensler, Francis C. Szoka Jr., "Polyamidoamine cascade polymers mediate efficient transfection of cells in culture," Bioconjugate Chemistry 4(September 1993):372-379.

1503. Julia Uppenbrink, "Completing the cycle," Science 284(18 June 1999):1942.

1504. K. Kim, "Mechanically interlocked molecules incorporating cucurbituril and their supramolecular assemblies," Chem. Soc. Rev. 31(March 2002):96-107.

1505. Y. Li, S.T. Lin, W.A. Goddard 3rd, "Efficiency of various lattices from hard ball to soft ball: theoretical study of thermodynamic properties of dendrimer liquid crystal from atomistic simulation," J. Am. Chem. Soc. 126(18 February 2004):1872-1885.

1506. D.A. Tomalia, H.M. Brothers 2nd, L.T. Piehler, H.D. Durst, D.R. Swanson, "Partial shell-filled core-shell tecto(dendrimers): a strategy to surface differentiated nano-clefts and cusps," Proc. Natl. Acad. Sci. (USA) 99(16 April 2002):5081-5087; http://www.pnas.org/cgi/content/full/99/8/5081.

1507. V. Percec, T.K. Bera, M. Glodde, Q. Fu, V.S. Balagurusamy, P.A. Heiney, "Hierarchical self-assembly, coassembly, and self-organization of novel liquid crystalline lattices and superlattices from a twin-tapered dendritic benzamide and its four-cylinder-bundle supramolecular polymer," Chemistry 9(17 February 2003):921-935; G. Ungar, Y. Liu, X. Zeng, V. Percec, W.D. Cho, "Giant supramolecular liquid crystal lattice," Science 299(21 February 2003):1208-1211.

1508. N.R. Luman, K.A. Smeds, M.W. Grinstaff, "The convergent synthesis of poly(glycerol-succinic acid) dendritic macromolecules," Chemistry 9(21 November 2003):5618-5626.

1509. T. Uchiyama, K. Ishii, T. Nonomura, N. Kobayashi, S. Isoda, "A phthalocyanine dendrimer capable of forming spherical micelles," Chemistry 9(5 December 2003):5757-5761.

1510. Fraser Stoddart, "Making molecules to order," Chem. in Britain 27(August 1991):714-718.

1511. Peter R. Ashton, Richard A. Bissell, Neil Spencer, J. Fraser Stoddart, Malcolm S. Tolley, "Towards controllable molecular shuttles," Synlett (November 1992):914-926.

1512. R.A. Bissell, E. Cordova, A.E. Kaifer, J.F. Stoddart, "A chemically and electrochemically switchable molecular shuttle," Nature 369(1994):133-137.

1513. Marcos Gomez-Lopez, Jon A. Preece, J. Fraser Stoddart, "The art and science of self-assembling molecular machines," Nanotechnology 7(September 1996):183-192.

1514. V.V. Balzani, A. Credi, F.M. Raymo, J.F. Stoddart, "Artificial molecular machines," Angew. Chem. Int. Ed. Engl. 39(2 October 2000):3348-3391.

1515. A.R. Pease, J.O. Jeppesen, J.F. Stoddart, Y. Luo, C.P. Collier, J.R. Heath, "Switching devices based on interlocked molecules," Acc. Chem. Res. 34(June 2001):433-444.

1516. G. Schill, Catenanes, Rotaxanes and Knots, Academic Press, New York, 1971. See also: D.B. Amabilino, J.F. Stoddart, "Interlocked and intertwined structures and superstructures," Chem. Rev. 95(1995):2725-2828.

1517. C.P. Collier, E.W. Wong, M. Belohradsky, F.M. Raymo, J.F. Stoddart, P.J. Kuekes, R.S. Williams, J.R. Heath, "Electronically configurable molecular-based logic gates," Science 285(16 July 1999):391-394, 313-314 (discussion).

1518. Gerhard Wenz, Bruno Keller, "Threading cyclodextrin rings on polymer chains," Angew. Chem. Int. Ed. Engl. 31(1992):197-199. See also: Ivan Amato, "The molecular bead game," Science 260(16 April 1993):293-294.

1519. H.W. Gibson, H. Marand, "Polyrotaxanes: molecular composites derived by physical linkage of cyclic and linear species," Advanced Materials 5(1993):11 et seq.

1520. A.S. Lane, D.A. Leigh, A. Murphy, "Peptide-based molecular shuttles," J. Am. Chem. Soc. 119(1997):11092-11093.

1521. D.A. Leigh, A. Murphy, J.P. Smart, A.M.Z. Slawin, "Glycylglycine rotaxanes — the hydrogen bond-directed assembly of synthetic peptide rotaxanes," Angew. Chem. Int. Ed. Engl. 36(1997):728-732.

1522. F.M. Raymo, J.F. Stoddart, "Polyrotaxanes and pseudopolyrotaxanes," Trends Polym. Sci. 4(1996):208-211.

1523. F.M. Raymo, J.F. Stoddart, "Slippage — a simple and efficient way to self-assemble [n]rotaxanes," Pure Appl. Chem. 69(1997):1987-1997.

1524. Roberto Ballardini, Vincenzo Balzani, Alberto Credi, Maria Teresa Gandolfi, Steven J. Langford, Stephan Menzer, Luca Prodi, J. Fraser Stoddart, Margherita Venturi, David J. Williams, "Simple molecular machines. Cyclical chemically-driven unthreading and re-threading of a [2]pseudorotaxane," Angew. Chem. Int. Ed. Engl. 35(1996):978-981.

1525. P.R. Ashton, et al., "Molecular Meccano. 24. Multiple stranded and multiply encircled pseudorotaxanes," J. Am. Chem. Soc. 119(1997):12514-12524.

1526. Guang Li, Linda B. McGown, "Molecular nanotube aggregates of beta- and gamma-cyclodextrins linked by diphenylhexatrienes," Science 264(8 April 1994):249-251.

1527. A. Harada, "Cyclodextrin-based molecular machines," Acc. Chem. Res. 34(June 2001):456-464.

1528. D.B. Amabilino, P.R. Ashton, A.S. Reder, N. Spencer, J.F. Stoddart, "The two-step self-assembly of [4]- and [5]-catenanes," Angew. Chem. Int. Ed. Engl. 33(1994):433-437. See also: "Another Gain in Self-Assembly," Science 265(29 July 1994):608.

1529. D.B. Amabilino, P.R. Ashton, S.E. Boyd, J.Y. Lee, S. Menzer, J.F. Stoddart, D.J. Williams, "The five-stage self-assembly of a branched heptacatenane," Angew. Chem. 109(1997):2160-2162; Angew. Chem. Int. Ed. Engl. 36(1997):2070-2072.

1530. Makoto Fujita, Norifumi Fujita, Katsuyuki Ogura, Kentaro Yamaguchi, "Spontaneous assembly of ten components into two interlocked identical coordination cages," Nature 400(1 July 1999):52-55.

1531. D.B. Amabilino, et al., "Molecular Meccano. 30. Oligocatenanes made to order," J. Am. Chem. Soc. 120(1998):4295-4307.

1532. P.R. Ashton, et al., "Supramolecular daisy chains," Angew. Chem 110(1998):1344-1347; Angew. Chem. Int. Ed. 37(1998):1294-1297.

1533. P.R. Ashton, et al., "Self-assembling supramolecular daisy chains," Angew. Chem. 110(1998):2016-2019; Angew. Chem. Int. Ed. 37(1998):1913-1916.

1534. F. Diederich, M. Gomez-Lopez, J.-F. Nierengarten, J.A. Preece, F.M. Raymo, J.F. Stoddart, "The self-assembly of the first fullerene-containing [2]catenane," Angew. Chem. 109(1997):1611-1614; Angew. Chem. Int. Ed. Engl. 36(1997):1448-1451.

1535. L.Z. Yan, P.E. Dawson, "Design and synthesis of a protein catenane," Angew. Chem. Int. Ed. Engl. 40(1 October 2001):3625-3627.

1536. P.R. Ashton, A.N. Collins, M.C.T. Fyfe, S. Menzer, J.F. Stoddart, D.J. Williams, "Supramolecular weaving," Angew. Chem. 109(1997):760-763; Angew. Chem. Int. Ed. Engl. 36(1997):735-739.

1537. A.G. Johnston, D.A. Leigh, R.J. Pritchard, M.D. Deegan, "Facile synthesis and solid state structure of a benzylic amide [2]catenane," Angew. Chem. Int. Ed. Engl. 34(1995):1209-1212.

1538. Judith Konnert, Doyle Britton, "The crystal structure of $AgC(CN)_3$," Inorg. Chem. 5(1966):1193-1196.

1539. David J. Duchamp, Richard E. Marsh, "The crystal structure of trimesic acid (benzene-1,3,5-tricarboxylic acid)," Acta Crystallogr. Sect. B 25(1969):5-19.

1540. Robert W. Gable, Bernard F. Hoskins, Richard Robson, "A new type of interpenetration involving enmeshed independent square grid sheets. The structure of diaquabis-(4,4'-bipyridine)zinc hexafluorosilicate," Chem. Commun. (1990):1677-1678.

1541. Humberto O. Stumpf, Lahcene Ouahab, Yu Pei, Daniel Grandjean, Olivier Kahn, "A molecular-based magnet with a fully interlocked three-dimensional structure," Science 261(23 July 1993):447-449. See also: Peter Day, "The chemistry of magnets," Science 261(23 July 1993):431-432.

1542. Jose Antonio Real, Enrique Andres, M. Carmen Munoz, Miguel Julve, Thierry Granier, Azzedine Bousseksou, Francois Varret, "Spin crossover in a catenane supramolecular system," Science 268(14 April 1995):265-267.

1543. Robert L. Duda, "Protein chain mail: Catenated protein in viral capsids," Cell 94(10 July 1998):55-60. See also: J. Travis, "Protein chain mail offers armor for viruses," Science News 154(18 July 1998):38.

1544. Saul Griffith, "Tools for designing programmatic self-assembling systems," Final Project Paper, Biologically Motivated Programming Technology for Robust Systems, MIT Course 6.978, December 2002; http://www.swiss.ai.mit.edu/projects/amorphous/6.978/final-papers/saul-final.pdf.

1545. "Chapter Four. Building Structures at the Nanoscale. 4.2 Self-Assembly," in Exploring the Nanoworld with LEGO® Bricks, University of Wisconsin, Madison Materials Research Science and Engineering Center (MRSEC) for Nanostructured Materials and Interfaces, Education and Outreach, 23 April 2003; http://mrsec.wisc.edu/edetc/LEGO/PDFfiles/bookchap4.pdf.

1546. K. Saitou, "Conformational switching in self-assembling mechanical systems," IEEE Transactions on Robotics and Automation 15(June 1999):510-520; http://www-personal.engin.umich.edu/~kazu/papers/tra-99.pdf.

1547. Kazuhiro Saitou, Mark J. Jakiela, "Automated optimal design of mechanical conformational switches," Artificial Life 2(Summer 1995):129-156; http://www-personal.engin.umich.edu/~kazu/papers/alifej-95a.pdf.

1548. Kazuhiro Saitou, Mark J. Jakiela, "Subassembly generation via mechanical conformational switches," Artificial Life 2(Summer 1995):377-416; http://www-personal.engin.umich.edu/~kazu/papers/alifej-95b.pdf.

1549. K. Saitou, M. Jakiela, "On classes of self-assembling automata," Complex Systems 10(1996):391-416; http://www-personal.engin.umich.edu/~kazu/papers/cs-98.pdf.

1550. K. Saitou, "Self-assembling automata: A model for conformational self-assembly," Proc. 1998 Pacific Symposium on Biocomputing, Maui, Hawaii, World Scientific, 1998, pp. 609-620; http://www-personal.engin.umich.edu/~kazu/papers/psb-98.pdf.

1551. K. Saitou, "Conformational switching as assembly instructions in self-assembling mechanical systems," Unifying Themes in Complex Systems: Proc. First Intl. Conf. on Complex Systems, Nashua, New Hampshire, Perseus Books, 1998, pp. 411-431; also available on-line via InterJournal of Complex Systems at: http://www.interjournal.org.

1552. K. Hosokawa, I. Shimoyama, H. Miura, "Dynamics of self-assembling systems: analogy with chemical kinetics," Artificial Life 1(1994):413-427; also in Artificial Life IV: Proc. 4th Intl. Workshop on the Synthesis and Simulation of Living Systems, Cambridge, MA, 6-8 July 1995, pp. 172-180.

1553. Radhika Nagpal, "Programmable Self-Assembly: Constructing Global Shape Using Biologically-Inspired Local Interactions and Origami Mathematics," MIT Artificial Intelligence Lab, June 2001; http://www.swiss.ai.mit.edu/projects/amorphous/Progmat/. See also: Radhika Nagpal, "Programmable Pattern-Formation and Scale-Independence," International Conference on Complex Systems (ICCS), June 2002, http://www.swiss.ai.mit.edu/projects/amorphous/papers/nagpal-ICCS2002.ps; Radhika Nagpal, "Programmable Self-Assembly Using Biologically-Inspired Multiagent Control," Proceedings of the 1st International Joint Conference on Autonomous Agents and Multi-Agent Systems (AAMAS), Bologna, Italy, July 2002, http://www.swiss.ai.mit.edu/projects/amorphous/papers/aamas02-nagpal.ps.

1554. Tad Hogg, Yong Chen, "Interfacing to Dense Nanowire Circuits with Self-Assembled Connectors," 11th Foresight Conference on Molecular Nanotechnology, October 2003; http://www.foresight.org/Conferences/MNT11/Abstracts/Hogg/index.html. See also: Tad Hogg, Yong Chen, Phil Kuekes, "Assembling Nanoscale Circuits with Randomized Connections," 7 August 2003, submitted for publication.

1555. Andre DeHon, Patrick Lincoln, John E. Savage, "Stochastic assembly of sublithographic nanoscale interfaces," preprint, July 2003.

1556. J. Liu, M. Casavant, M. Cox, D.A. Walters, P. Boul, W. Lu, A.J. Rimberg, K. Smith, D.T. Colbert, R.E. Smalley, "Controlled deposition of individual single-walled carbon nanotubes on chemically functionalized templates," Chem. Phys. Lett. 303(2 April 1999):125-129; http://www.ruf.rice.edu/~smalleyg/rick's%20publications/CPL303-125.pdf.

1557. Jia Liu, Takhee Lee, B.L. Walsh, R.P. Andres, D.B. Janes, M.R. Melloch, J.M. Woodall, R. Reifenberger, "Guided self-assembly of Au nanocluster arrays electronically coupled to semiconductor device layers," Appl. Phys.Lett. 77(2000):373; http://www.eng.yale.edu/reedlab/people/takhee/pdf//liu-APL00.pdf.

1558. Xiao M. Yang, Richard D. Peters, Paul F. Nealey, Harun H. Solak, Franco Cerrina, "Guided self-assembly of symmetric diblock copolymer films on chemically nanopatterned substrates," Macromolecules 33(26 December 2000):9575-9582. See also: Xiao M. Yang, Richard D. Peters, Qiang Wang, Juan de Pablo, Paul Nealey, "Guided self-assembly of the domain structure in thin films of diblock copolymers using substrates patterned with nanolithography," AIChE 2000 Annual Meeting, Los Angeles, CA, November 2000; http://aiche.org/conferences/techprogram/paperdetail.asp?PaperID=1464&DSN=annual2k (abstract).

1559. Ward A. Lopes, H.M. Jaeger, "Hierarchical self-assembly of metal nanostructures on diblock copolymer scaffolds," Nature 414(13 December 2001):735-738; http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v414/n6865/abs/414735a_r.html (abstract).

1560. H.H. Solak, C. David, J. Gobrecht, S.O. Kim, P.F. Nealey, "Guided self-assembly of copolymer films on templates patterned with x-ray interference lithography," PSA Scientific Report 2002, Volume VII, Laboratory for Micro- and Nanotechnology, Paul Scherrer Institut, Switzerland; http://lmn.web.psi.ch/annrep/xr0306.pdf.

1561. P. Mesquida, A. Stemmer, "Guiding self-assembly with the tip of an atomic force microscope," Scanning 24(May-June 2002):117-120.

1562. Chris Dwyer, Russell Taylor, Richard Superfine, Sean Washburn, Dorothy Erie, "Methodology for the DNA-guided self-assembly of novel computing circuitry," paper presented at the 10th Foresight Conference on Molecular Nanotechnology, October 2002; http://www.foresight.org/Conferences/MNT10/Abstracts/Dwyer/.

1563. Y.F. Gao, Z. Suo, "Guided self-assembly of molecular dipoles on a substrate surface," J. Appl. Phys. 93(2003):4276; http://beijing.princeton.edu/~yfgao/140.pdf.

1564. Jiyun C. Huie, "Guided molecular self-assembly: a review of recent efforts," Smart Mater. Struct. 12(April 2003):264-271; http://www.iop.org/EJ/S/UNREG/IZE8m1SUw3kCRD6cLEeVPQ/abstract/0964-1726/12/2/315 (abstract).

1565. Tad Hogg, "Robust self-assembly using highly designable structures," Nanotechnology 10(September 1999):300-307. See also: Tad Hogg, "Robust self-assembly using highly designable structures," presentation at the Sixth Foresight Nanotechnology Conference, November 1998; see at: http://www.foresight.org/Conferences/MNT6/Papers/Hogg/index.html or http://einstein.sc.mahidol.ac.th/nanotech/course/pdf/robust-selfassem.pdf.

1566. P.W.K. Rothemund, E. Winfree, "The program-size complexity of self-assembled squares," Proc. 32nd Annual ACM Symp. On Theory of Computing (STOC 2000), ACM, New York, 2000, pp. 459-468; http://www.dna.caltech.edu/Papers/squares_STOC.ps.

1567. Jarle Breivik, "Self-organization of template-replicating polymers and the spontaneous rise of genetic information," Entropy 3(20 November 2001):273-279; http://www.mdpi.org/entropy/papers/e3040273.pdf. See also: Vivo Innovation: Interactive Life Science — Self-Replicating Polymers, 2000; http://www.vivo-innovation.com/.

1568. David H. Gracias, Joe Tien, Tricia L. Breen, Carey Hsu, George M. Whitesides, "Forming electrical networks in three dimensions by self-assembly," Science 289(18 August 2000):1170-1172; http://people.bu.edu/jtien/Gracias_Sci_2000_289_1170.pdf.

1569. Insung S. Choi, Ned Bowden, George M. Whitesides, "Macroscopic, hierarchical, two-dimensional self-assembly," Angew. Chem. Int. Ed. Engl. 38(1999):3078-3081.

1570. N. Bowden, A. Terfort, J. Carbeck, G.M. Whitesides, "Self-assembly of mesoscale objects into ordered two-dimensional arrays," Science 276(11 April 1997):233-235.

1571. A. Terfort, N. Bowden, G.M. Whitesides, "Three-dimensional self-assembly of millimeter-scale components," Nature 386(1997):162-164.

1572. Paul W.K. Rothemund, "Using lateral capillary forces to compute by self-assembly," Proc. Natl. Acad. Sci. (USA) 97(1 February 2000):984-989.

1573. T.D. Clark, M. Boncheva, J.M. German, M. Weck, G.M. Whitesides, "Design of three dimensional, millimeter-scale models for molecular folding," J. Am. Chem. Soc. 124(2002):18-19.

1574. J. Tien, T.L. Breen, G.M. Whitesides, "Crystallization of millimeter-scale objects with use of capillary forces," J. Am. Chem. Soc. 120(1998):12670-12671.

1575. Hongkai Wu, N. Bowden, G.M. Whitesides, "Selectivities among capillary bonds in mesoscale self-assembly," Appl. Phys. Lett. 75(15 November 1999):3222-3224.

1576. N. Bowden, I.S. Choi, B.A. Grzybowski, G.M. Whitesides, "Mesoscale self-assembly of hexagonal plates using lateral capillary forces: synthesis using the 'capillary bond'," J. Am. Chem. Soc. 121(1999):5373-5391.

1577. I.S. Choi, M. Weck, B. Xu, N.L. Jeon, G.M. Whitesides, "Mesoscopic, templated self-assembly at the fluid-fluid interface," Langmuir 16(2000):2997-2999.

1578. S.R.J. Oliver, T.D. Clark, N. Bowden, G.M. Whitesides, "Three-dimensional self-assembly of complex, millimeter-scale structures through capillary bonding," J. Am. Chem. Soc. 123(2001):8119-8120.

1579. N. Bowden, F. Arias, T. Deng, G.M. Whitesides, "Self-assembly of microscale objects at a liquid/liquid interface through lateral capillary forces," Langmuir 17(2001):1757-1765.

1580. J. Tien, A. Terfort, G.M. Whitesides, "Microfabrication through electrostatic self-assembly," Langmuir 13(1997):5349-5355.

1581. R.S. Fearing, "Micro structures and micro actuators for implementing sub-millimeter robots," in H.S. Tzou, T. Fukuda, eds., Precision Sensors, Actuators and Systems, Kluwer Academic Publishers, Boston MA, 1992, pp. 39-72.

1582. E. Shimada, J.A. Thompson, J. Yan, R.J. Wood, R.S. Fearing, "Prototyping millirobots using dexterous microassembly and folding," Symposium on Microrobotics, ASME Int. Mechanical Engineering Cong. and Exp., Orlando, FL, 5-10 November 2000, DSC-Vol. 69-2, pp. 933-940; http://robotics.eecs.berkeley.edu/~ronf/PAPERS/mumanip.pdf.

1583. M. Weck, I.S. Choi, N.L. Jeon, G.M. Whitesides, "Assembly of mesoscopic analogues of nucleic acids," J. Am. Chem. Soc. 122(2000):3546-3547.

1584. H.R. Crane, "Principles and problems of biological growth," Scientific Monthly 70(June 1950):376-389.

1585. M. Calvin, Chemical Evolution, Oxford Press, 1969.

1586. Arthur Winfree, "Rotating chemical reactions," Sci. Am. 230(June 1974):82-95; A.T. Winfree, "The prehistory of the Belousov-Zhabotinsky oscillator," J. Chem. Educ. 61(1984):661-663.

1587. B.J. Welsh, J. Gomatam, A.E. Burgess, "Three-dimensional chemical waves in the Belousov-Zhabotinskii reaction," Nature 304(1983):611-614.

1588. John J. Tyson, The Belousov-Zhabotinskii Reaction, Springer-Verlag, New York, 1976; John J. Tyson, "What everyone should know about the Belousov-Zhabotinsky Reaction," in S.A. Levin, ed., Lecture Notes in Biomathematics, Vol. 100, Springer-Verlag, New York, 1994, pp. 569-587.

1589. "The Belousov-Zhabotinskii Reaction," see http://staff.science.nus.edu.sg/~parwani/c1/node65.html and http://www.zoo.co.uk/~z0001246/zhab.html; see also "Picture Gallery" at http://www.chem.leeds.ac.uk/chaos/pic_gal.html.

1590. Q. Ouyang, H.L. Swinney, G. Li, "Transition from spirals to defect-mediated turbulence driven by a Doppler instability," Phys. Rev. Lett. 84(31 January 2000):1047-1050.

1591. R.J. Field, E. Ko'ros, Richard Macy Noyes, "Oscillations in chemical systems. II. Thorough analysis of temporal oscillations in the bromate-cerium-malonic acid system," J. Am. Chem. Soc. 94(1972):8649-8664; Richard Macy Noyes, R.J. Field, "Oscillations in chemical systems. V. Quantitative explanation of band migration in the Belousov-Zhabotinskii reaction," J. Am. Chem. Soc. 96(1978):2001-2006; R.M. Noyes, "Some models of chemical oscillators," J. Chem. Educ. 66(1989):190-191.

1592. P. Gray, S.K. Scott, "Autocatalytic reactions in isothermal, continuous stirred tank reactor: oscillations and instabilities in the system A+2B → 3B,B → C," Chem. Eng. Sci. 39(1984):1087-1097. See also: "Gray Scott Model of Reaction Diffusion," http://www.swiss.ai.mit.edu/projects/amorphous/GrayScott/.

1593. John E. Pearson, "Complex patterns in a simple system," Science 261(9 July 1993):189-192; W.N. Reynolds, J.E. Pearson, S. Ponce-Dawson, "Dynamics of self-replicating pattern in reaction-diffusion systems," Phys. Rev. Lett. 72(1994):2797-2800; W.N. Reynolds, S. Ponce-Dawson, J.E. Pearson, "Self-replicating spots in reaction-diffusion systems," Phys. Rev. E 56(1997):185-198.

1594. K.J. Lee, W.D. McCormick, Qi Ouyang, H.L. Swinney, "Pattern formation by interacting chemical fronts," Science 261(9 July 1993):192-194; K.J. Lee, W.D. McCormick, J.E. Pearson, H.L. Swinney, "Experimental observation of self-replicating spots in a reaction-diffusion system," Nature 369(1994):215-218; D. Haim, G. Li, Q. Ouyang, W.D. McCormick, H.L. Swinney, A. Hagberg, E. Meron, "Breathing spots in a reaction-diffusion system," Phys. Rev. Lett. 77(1 July 1996):190-193.

1595. V. Petrov, S.K. Scott, K. Showalter, "Excitability, wave reflection, and wave splitting in a cubic autocatalysis reaction-diffusion system," Phil. Trans. R. Soc. Lond. A 347(1994):631-642.

1596. K.J. Lee, H.L. Swinney, "Lamellar structures and self-replicating spots in a reaction-diffusion system," Phys. Rev. E. 51(March 1995):1899-1915.

1597. K.E. Rasmussen, W. Mazin, E. Mosekilde, G. Dewel, P. Borckmans, "Wave-splitting in the bistable Gray-Scott model," Int. J. Bifurcation and Chaos 6(1996):1077-1092.

1598. Y. Nishiura, D. Ueyama, "A skeleton structure of self-replicating dynamics," Physica D 130(1999):73-104.

1599. H. Takagi, K. Kaneko, "Differentiation and replication of spots in a reaction-diffusion system with many chemicals," Europhys. Lett. 56(April 2001):145-151; http://chaos.c.u-tokyo.ac.jp/~takagi/GS-submit.ps.gz.

1600. F. Lesmes, D. Hochberg, F. Moran, J. Perez-Mercader, "Noise-controlled self-replicating patterns," Phys. Rev. Lett. 91(5 December 2003):238301.

1601. P. De Kepper, J.J. Perraud, B. Rudovics, E. Dulos, "Experimental study of stationary Turing patterns and their interaction with traveling waves in a chemical system," Int. J. Bifurcation and Chaos 6(1994):1077-1092.

1602. V. Castets, E. Dulos, J. Boissonade, P. de Kepper, "Experimental evidence of a sustained standing Turing-type nonequilibrium chemical pattern," Phys. Rev. Lett. 64(1990):2953-2956.

1603. A.T. Winfree, "Crystals from dreams," Nature 352(15 August 1991):568-569; http://cochise.biosci.arizona.edu/~art/dreams.pdf.

1604. Q. Ouyang, Harry L. Swinney, "Transition from a uniform state to hexagonal and striped Turing patterns," Nature 352(1991):610-612.

1605. I. Lengyel, S. Kadar, I.R. Epstein, "Transient Turing structures in a gradient-free closed system," Science 259(1993):493-495.

1606. J. Ross, Adam P. Arkin, S.C. Muller, "Experimental evidence for Turing structures," J. Amer. Chem. Soc. 99(1995):10417-10419.

1607. Enrique Peacock-Lopez, Geoffrey Hutchison, Leo L. Tsai, "Turing patterns in a self-replicating mechanism with a self-complementary template," J. Chem. Phys. 113(2000):6512-6515.

1608. Matthias Weiss, "Stabilizing Turing patterns with subdiffusion in systems with low particle numbers," Phys. Rev. E 68(2003):036213.

1609. Raymond Kapral, Kenneth Showalter, eds., Chemical Waves and Patterns, Understanding Chemical Reactivity, Vol. 10, Kluwer Academic Publishers, New York, 1995.

1610. Richard J. Field, Maria Burger, Oscillations and Traveling Waves in Chemical Systems, Wiley-Interscience, New York, 1985.

1611. I.R. Epstein, K. Kustin, P. De Kepper, M. Orban, "Oscillating chemical reactions," Sci. Am. 248(March 1983):112-123; I.R. Epstein, "Patterns in time and space — generated by chemistry," Chem. & Eng. News, 30 March 1987, pp. 24-36.

1612. S.K. Scott, Oscillations, Waves, and Chaos in Chemical Kinetics, Oxford Science Publications, Oxford, 1994.

1613. Kunihiko Kaneko, "Recursiveness, switching, and fluctuations in a replicating catalytic network," Phys. Rev. E 68(2003):031909.

1614. Alan M. Turing, "The chemical basis of morphogenesis," Phil Trans. Roy. Soc. London Ser. B: Biol. Sci. 237(1952):37-72.

1615. Philip Ball, "The robot within," New Scientist Magazine, 15 March 2003; http://www.newscientist.com/hottopics/dna/article.jsp?id=23865500&sub=DNA:%20the%20next%2050%20years.

1616. J. Rebek, "Molecular recognition with model systems," Angew. Chem. Int. Ed. Engl. 29(1990):245-255.

1617. James S. Nowick, Qing Feng, Tjama Tjivikua, Pablo Ballester, Julius Rebek, Jr., "Kinetic studies and modeling of a self-replicating system," J. Am. Chem. Soc. 113(1991):8831-8839.

1618. J.I. Hong, Q. Feng, V. Rotello, J. Rebek, "Competition, cooperation, and mutation: Improving a synthetic replicator by light irradiation," Science 255(1992):848-850.

1619. Julius Rebek, Jr., "Synthetic self-replicating molecules," Sci. Amer. 271(July 1994):48-55.

1620. T. Tjivikua, P. Ballester, J. Rebek, Jr., "A self-replicating system," J. Am. Chem. Soc. 112(31 January 1990):1249-1250.

1621. A. Terfort, G. von Kiedrowski, "Self-replication by condensation of 3-amino-benzamidines and 2-formylphenoxyacetic acids," Angew. Chem. Int. Ed. Engl. 31(May 1992):654-656.

1622. E.A. Wintner, M.M. Conn, J. Rebek Jr., "Self-replicating molecules — a 2nd generation," J. Am. Chem. Soc. 116(5 October 1994):8877-8884.

1623. V.C. Allen, D. Philp, N. Spencer, "Transfer of stereochemical information in a minimal self-replicating system," Org. Lett. 3(8 March 2001):777-780.

1624. E.K. O'Shea, J.D. Klemm, P.S. Kim, T. Alber, "X-ray structure of the GCN4 leucine zipper, a two-stranded, parallel coiled coil," Science 254(25 October 1991):539-544; P.B. Harbury, T. Zhang, P.S. Kim, T. Alber, "A switch between two-, three-, and four-stranded coiled coils in GCN4 leucine zipper mutants," Science 262(26 November 1993):1401-1407.

1625. Stuart A. Kauffman, "Cellular homeostasis, epigenesis and replication in randomly aggregated macromolecular systems," J. Cybernetics 1(1971):71-96.

1626. Stuart A. Kauffman, "Autocatalytic sets of proteins," J. Theor. Biol. 119(7 March 1986):1-24.

1627. Stuart A. Kauffman, "Self-replication: Even peptides do it," Nature 382(8 August 1996):496-497; http://www.santafe.edu/sfi/People/kauffman/sak-peptides.html.

1628. J.D. Farmer, S.A. Kauffman, N.H. Packard, "Autocatalytic replication of polymers," Physica D 22(1986):50-67.

1629. J.D. Farmer, N.H. Packard, A.S. Perelson, "The immune system, adaptation, and machine learning," Physica D 22(1986):187-204.

1630. Richard J. Bagley, J. Doyne Farmer, "Spontaneous emergence of a metabolism," in C. Langdon, C. Taylor, J. Farmer, S. Rasmussen, eds., Artificial Life II, Addison-Wesley, New York, 1992, pp. 93-140.

1631. R.J. Bagley, J.D. Farmer, S.A. Kauffman, N.H. Packard, A.S. Perelson, I.M. Stadnyk, "Modeling adaptive biological systems," Biosystems 23(1989):113-138.

1632. R.J. Bagley, J.D. Farmer, W. Fontana, "Evolution of a metabolism," in C. Langdon, C. Taylor, J. Farmer, S. Rasmussen, eds., Artificial Life II, Addison-Wesley, New York, 1992, pp. 141-158.

1633. Wolfgang Banzhaf, "Self-organization in a system of binary strings," in R. Brooks, P. Maes, eds., Proceedings of Artificial Life IV, MIT Press, Cambridge, MA, 1994, pp. 109-118; http://ls11-www.informatik.uni-dortmund.de/people/banzhaf/alife94.ps.gz.

1634. Peter Dittrich, Wolfgang Banzhaf, "Self-evolution in a constructive binary string system," Artificial Life 4(1998):203-220; http://ls11-www.informatik.uni-dortmund.de/people/dittrich//p/DB97alife.ps.

1635. Wolfgang Banzhaf, Peter Dittrich, Burkhard Eller, "Self-organization in a system of binary strings with topological interactions," Physica D 125(1999):85-104; http://ls11-www.informatik.uni-dortmund.de/people/dittrich//p/BDE98.html (abstract), http://ls11-www.informatik.uni-dortmund.de/people/banzhaf/physica_d2.pdf (paper).

1636. Pietro Speroni di Fenizio, Peter Dittrich, Wolfgang Banzhaf, "Spontaneous formation of proto-cells in a universal artificial chemistry on a planar graph," in J. Kemelen, P. Sosik, eds., Advances in Artificial Life, Proc. of the 6th European Conf. (ECAL 2001), Prague, September 2001, pp. 206-215; http://ls11-www.informatik.uni-dortmund.de/people/banzhaf/ecal01_spont.ps.gz.

1637. Peter Dittrich, Jens Ziegler, Wolfgang Banzhaf, "Artificial chemistries — a review," Artificial Life 7(2001):225-275; see http://ls11-www.informatik.uni-dortmund.de/people/banzhaf/ac_review.pdf.

1638. Jens Ziegler, Wolfgang Banzhaf, "Evolving control metabolisms for a robot," Artificial Life 7(2001):171-190; http://ls11-www.informatik.uni-dortmund.de/people/banzhaf/metabolism.pdf.

1639. M.C. Boerlijst, P. Hogeweg, "Spatial gradients enhance persistence of hypercycles," Physica D 88(1988):29-39; M.C. Boerlijst, P. Hogeweg, "Spiral wave structure in prebiotic evolution: Hypercycles stable against parasites," Physica D 48(1991):17-28.

1640. G.R. Cousins, S.A. Poulsen, J.K. Sanders, "Molecular evolution: dynamic combinatorial libraries, autocatalytic networks and the quest for molecular function," Curr. Opin. Chem. Biol. 4(June 2000):270-279.

1641. Tibor Ganti (Eors Szathmary, James Griesemer, eds.), The Principles of Life, Oxford University Press, New York, 2003; Tibor Ganti, The Principle of Life, Gondolat, Budapest, 1971. (In Hungarian).

1642. T. Ganti, "Organization of chemical reactions into dividing and metabolizing units: the chemotons," BioSystems 7(1975):189-195.

1643. T. Ganti, "Chemical systems and supersystems. III. Models of self-reproducing chemical supersystems: the chemotons," Acta Chim. Acad. Sci. Hung. 98(1978):265-283.

1644. Tibor Ganti, A Theory of Biochemical Supersystems and its Application to Problems of Natural and Artificial Biogenesis, University Park Press, Baltimore, MD, 1979.

1645. T. Ganti, Chemoton Theory I. Theoretical Foundations of Fluid Machineries, OMIKK, Budapest, 1984. In Hungarian.

1646. Tibor Ganti, "Biogenesis itself," J. Theor. Biol. 187(1997):583-593.

1647. J. Hofbauer, K. Sigmund, The theory of evolution and dynamical systems, Cambridge University Press, Cambridge, U.K., 1988.

1648. Steen Rasmussen, "Toward a quantitative theory of the origin of life," in Christopher G. Langton, ed., Artificial Life, Studies in the Sciences of Complexity, Santa Fe Institute, Volume VI, Addison-Wesley, New York, 1989, pp. 79-104.

1649. O. Rossler, "A system theoretic model of biogenesis," Z. Naturforsch. B26b(1971):741-746; "Deductive prebiology," in K.L. Rolfing, ed., Molecular Evolution and the Prebiological Paradigm, Plenum, New York, 1983.

1650. P. Schuster, "Dynamics of autocatalytic reaction networks," in A. Perelson, S. Kauffman, eds., Molecular Evolution on Rugged Landscapes, Studies in the Sciences of Complexity, Proc. Vol. IX, Addison-Wesley, Redwood City, CA, 1990, pp. 281-306.

1651. P.F. Stadler, "Dynamics of autocatalytic reaction networks. IV: Inhomogeneous replicator networks," Biosystems 26(1991):1-19.

1652. P.F. Stadler, R. Happel, "The probability of permanence," Math. Biosci. 113(January 1993):25-50.

1653. P.F. Stadler, W. Fontana, J.H. Miller, "Random catalytic reaction networks," Physica E 63(1993):378-392.

1654. P.F. Stadler, J.C. Nuno, "The influence of mutation on autocatalytic reaction networks," Math. Biosci. 122(August 1994):127-160.

1655. R. Hecht, R. Happel, P. Schuster, P.F. Stadler, "Autocatalytic networks with intermediates. I: Irreversible reactions," Math. Biosci. 140(February 1997):33-74.

1656. B.M. Stadler, P.F. Stadler, P. Schuster, "Dynamics of autocatalytic replicator networks based on higher-order ligation reactions," Bull. Math. Biol. 62(November 2000):1061-1086.

1657. D. Stassinopoulos, S.P. Colombano, J.D. Lohn, G.L. Haith, J. Scargle, S. Liang, "Spatial autocatalytic dynamics: an approach to modeling prebiotic evolution," Proc. 1998 Intl. Conf. on Complex Systems, Nashua NH, 1998; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/necsi1998.pdf.

1658. J.D. Lohn, S.P. Colombano, J. Scargle, D. Stassinopoulos, G. L. Haith, "Evolution of catalytic reaction sets using genetic algorithms," IEEE Intl. Conf. on Evolutionary Computation, 1998, pp. 487-492; http://ic.arc.nasa.gov/ic/people/jlohn/Papers/icec1998.pdf.

1659. L. Varetto, "Studying artificial life with a molecular automaton," J. Theor. Biol. 193(27 July 1998):257-285.

1660. D. Sievers, G. von Kiedrowski, "Self-Replication of Hexadeoxynucleotide Analogues: Autocatalysis versus Cross-Catalysis," Chem. Eur. J. 4(1998):629-641.

1661. G. Wachtershauser, "Groundworks for an evolutionary biochemistry: the iron-sulphur world," Prog. Biophys. Molec. Biol. 58(1992):85-201.

1662. M. Eigen, "Self-organization of matter and the evolution of biological macromolecules," Naturwissenschaften 58(1971):465-523.

1663. M. Eigen, P. Schuster, The Hypercycle: A Principle of Natural Self-Organization, Springer-Verlag, New York, 1979; "The hypercycle. A principle of natural self-organization. Part A: Emergence of the hypercycle," Naturwissenschaften 64(November 1977):541-565.

1664. G.A. King, "Growth of a hypercycle and comparison with conventional autocatalysis," Biosystems 13(1981):225-234; M. Eigen, P. Schuster, "Comments on 'growth of a hypercycle' by King (1981)," Biosystems 13(1981):235.

1665. P. Schuster, "Polynucleotide evolution, hypercycles and the origin of the genetic code," Adv. Space Res. 4(1984):143-151.

1666. M. Eigen, C.K. Biebricher, M. Gebinoga, W.C. Gardiner, "The hypercycle. Coupling of RNA and protein biosynthesis in the infection cycle of an RNA bacteriophage," Biochemistry 30(19 November 1991):11005-11018.

1667. M.B. Cronhjort, "Hypercycles versus parasites in the origin of life: model dependence in spatial hypercycle systems," Orig. Life Evol. Biosph. 25(June 1995):227-233.

1668. M. Ycas, "Codons and hypercycles," Orig. Life Evol. Biosph. 29(January 1999):95-108.

1669. A.U. Igamberdiev, "Foundations of metabolic organization: coherence as a basis of computational properties in metabolic networks," Biosystems 50(April 1999):1-16.

1670. P.R. Campos, J.F. Fontanari, P.F. Stadler, "Error propagation in the hypercycle," Phys. Rev. E Stat. Phys. Plasmas Fluids Relat. Interdiscip. Topics 61(March 2000):2996-3002.

1671. A. Saghatelian, Y. Yokobayashi, K. Soltani, M.R. Ghadiri, "A chiroselective peptide replicator," Nature 409(15 February 2001):797-801, 777-8 (comment).

1672. M. Reza Ghadiri, "Molecular self-assembly, self-organization, and self-replication," presentation at the Sixth Foresight Conference on Molecular Nanotechnology, November 1998.

1673. Martin C. Wright, Gerald F. Joyce, "Continuous in vitro evolution of catalytic function," Science 276(25 April 1997):614-617.

1674. T. Li, K.C. Nicolaou, "Chemical self-replication of palindromic duplex DNA," Nature 369(19 May 1994):218-21, 184-185 (comment).

1675. E. Westhof, B. Masquida, L. Jaeger, "RNA tectonics: towards RNA design," Structure, Folding and Design 1(1996):78-88.

1676. L. Jaeger, N.B. Leontis, "Tecto-RNA: One-dimensional Self-assembly through Tertiary Interactions," Angew. Chem. Int. Ed. Engl. 39(2000):2521-2524; Angew. Chem. 112(2000):2576-2580.

1677. L. Jaeger, E. Westhof, N.B. Leontis, "TectoRNA: Modular assembly units for the construction of RNA nano-objects," Nucleic Acids Res. 29(2001):455-463.

1678. Luc Jaeger, Arkadiusz Chworos, "How to play LEGO with RNA: design of RNA cellular automata," 11th Foresight Conference on Molecular Nanotechnology, Palo Alto, CA, 9-12 October 2003; http://www.foresight.org/Conferences/MNT11/Abstracts/Jaeger/index.html.

1679. J.E. Padilla, C. Colovos, T.O. Yeates, "Nanohedra: using symmetry to design self assembling protein cages, layers, crystals, and filaments," Proc. Natl. Acad. Sci. (USA) 98(27 February 2001):2217-2221; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11226219&dopt=Abstract.

1680. Robert K. Murray, Daryl K. Granner, Peter A. Mayes, Victor W. Rodwell, Harper's Biochemistry, 23rd Edition, Appleton & Lange, Norwalk CT, 1993.

1681. H.F. Noller, V. Hoffarth, L. Zimniak, "Unusual resistance of peptidyl transferase to protein extraction procedures," Science 256(5 June 1992):1416-1419, 1396-1397 (comment), 1402-1403 (comment).

1682. P. Nissen, J. Hansen, N. Ban, P.B. Moore, T.A. Steitz, "The structural basis of ribosome activity in peptide bond synthesis," Science 289(11 August 2000):920-930, 878-879 (comment).

1683. J.D. Puglisi, S.C. Blanchard, R. Green, "Approaching translation at atomic resolution," Nat. Struct. Biol. 7(October 2000):855-861; Nat. Struct. Biol. 8(February 2001):109 (comment).

1684. R. Green, H.F. Noller, "Ribosomes and translation," Annu. Rev. Biochem. 66(1997):679-716.

1685. J.H. Cate, M.M. Yusupov, G.Z. Yusupova, T.N. Earnest, H.F. Noller, "X-ray crystal structures of 70S ribosome functional complexes," Science 285(24 September 1999):2095-2104, 2048-2051 (comment), 2077-2078 (comment).

1686. J. Frank, R.K. Agrawal, "A ratchet-like inter-subunit reorganization of the ribosome during translocation," Nature 406(20 July 2000):318-322.

1687. M.W. Gray, D. Sankoff, R.J. Cedergren, "On the evolutionary descent of organisms and organelles: a global phylogeny based on a highly conserved structural core in small subunit ribosomal RNA," Nucleic Acids Res. 12(25 July 1984):5837-5852.

1688. Marat M. Yusupov, Gulnara Zh. Yusupova, Albion Baucom, Kate Lieberman, Thomas N. Earnest, J.H.D. Cate, Harry F. Noller, "Crystal structure of the ribosome at 5.5 A resolution," Science 292(4 May 2001):883-896.

1689. J. Frank, A. Verschoor, Y. Li, J. Zhu, R.K. Lata, M. Radermacher, P. Penczek, R. Grassucci, R.K. Agrawal, S. Srivastava, "A model of the translational apparatus based on a three-dimensional reconstruction of the *Escherichia coli* ribosome," Biochem. Cell Biol. 73(November-December 1995):757-765.

1690. Walter E. Hill, ed., The Ribosome: Structure, Function, and Evolution, American Society for Microbiology, Washington, DC, 1990.

1691. A.T. Matheson, P.P. Dennis, J.E. Davies, W.E. Hill, "Frontiers in translation. An international conference on the structure and function of the ribosome," Biochem. Cell Biol. 73(November-December 1995):iv, 739-1227.

1692. R.A. Garrett, Stephen R. Douthwaite, Anders Liljas, Peter B. Moore, Harry F. Noller, Alistair T. Matheson, eds., The Ribosome: Structure, Function, Antibiotics, and Cellular Interactions, American Society for Microbiology, Washington, DC, 2000.

1693. Benjamin Lewin, Genes V, Oxford University Press, New York, 1995.

1694. J.D. Watson, N.H. Hopkins, J.W. Roberts, J.A. Steitz, A.M. Weiner, Molecular Biology of the Gene, Fourth edition, Benjamin/Cummings, Menlo Park, CA, 1987.

1695. Bruce Alberts, Dennis Bray, Julian Lewis, Martin Raff, Keith Roberts, James D. Watson, The Molecular Biology of the Cell, Second Edition, Garland Publishing, Inc., New York, 1989.

1696. B.T. Wimberly, D.E. Brodersen, W.M. Clemons Jr., R.J. Morgan-Warren, A.P. Carter, C. Vonrhein, T. Hartsch, V. Ramakrishnan, "Structure of the 30S ribosomal subunit," Nature 407(21 September 2000):327-339, 306-307 (comment).

1697. Dan Heidel, internet posting, 1999; cited in Robert A. Freitas Jr., Nanomedicine, Volume I: Basic Capabilities, Landes Bioscience, Georgetown, TX, 1999, pp. 43-44.

1698. P.J. Beuning, K. Musier-Forsyth, "Transfer RNA recognition by aminoacyl-tRNA synthetases," Biopolymers 52(1999):1-28.

1699. K.H. Nierhaus, D. Beyer, M. Dabrowski, M.A. Schafer, C.M. Spahn, J. Wadzack, J.U. Bittner, N. Burkhardt, G. Diedrich, R. Junemann, et al, "The elongating ribosome: structural and functional aspects," Biochem. Cell. Biol. 73(November-December 1995):1011-1021.

1700. K.P. Williams, D.P. Bartel, "Phylogenetic analysis of tmRNA secondary structure," RNA 2(1996):1306-1310. See also: "The tmRNA Website", http://www.indiana.edu/~tmrna/.

1701. R.L. Gourse, T. Gaal, M.S. Bartlett, J.A. Appleman, W. Ross, "rRNA transcription and growth rate-dependent regulation of ribosome synthesis in Escherichia coli," Annu. Rev. Microbiol. 50(1996):645-677.

1702. M.R. Paule, R.J. White, "Survey and summary: transcription by RNA polymerases I and III," Nucleic Acids Res. 28(15 March 2000):1283-1298.

1703. Y. Huang, R.J. Maraia, "Comparison of the RNA polymerase III transcription machinery in Schizosaccharomyces pombe, Saccharomyces cerevisiae and human," Nucleic Acids Res. 29(1 July 2001):2675-2690; Nucleic Acids Res. 29(15 August 2001):2 (erratum).

1704. P. Khaitovich, A.S. Mankin, "Effect of antibiotics on large ribosomal subunit assembly reveals possible function of 5 S rRNA," J. Mol. Biol. 291(3 September 1999):1025-1034.

1705. S.C. Agalarov, J.R. Williamson, "A hierarchy of RNA subdomains in assembly of the central domain of the 30 S ribosomal subunit," RNA 6(March 2000):402-408.

1706. S.C. Agalarov, G. Sridhar Prasad, P.M. Funke, C.D. Stout, J.R. Williamson, "Structure of the S15,S6,S18-rRNA complex: assembly of the 30S ribosome central domain," Science 288(7 April 2000):107-113.

1707. Jan Genzer, Kirill Efimenko, "Creating long-lived superhydrophobic polymer surfaces through mechanically assembled monolayers," Science 290(15 December 2000):2130-2132.

1708. D.E. Cane, C.T. Walsh, "The parallel and convergent universes of polyketide synthases and nonribosomal peptide synthetases," Chem. Biol. 6(December 1999):R319-R325.

1709. C. Khosla, R.S. Gokhale, J.R. Jacobsen, D.E. Cane, "Tolerance and specificity of polyketide synthases," Annu. Rev. Biochem. 68(1999):219-253.

1710. L.E. Quadri, "Assembly of aryl-capped siderophores by modular peptide synthetases and polyketide synthases," Mol. Microbiol. 37(July 2000):1-12.

1711. H.D. Mootz, M.A. Marahiel, "Design and application of multimodular peptide synthetases," Curr. Opin. Biotechnol. 10(August 1999):341-348.

1712. D.E. Cane, C.T. Walsh, "The parallel and convergent universes of polyketide synthases and nonribosomal peptide synthetases," Chem. Biol. 6(December 1999):R319-R325.

1713. J. Staunton, B. Wilkinson, "Combinatorial biosynthesis of polyketides and nonribosomal peptides," Curr. Opin. Chem. Biol. 5(April 2001):159-164.

1714. H.D. Mootz, D. Schwarzer, M.A. Marahiel, "Ways of assembling complex natural products on modular nonribosomal peptide synthetases," Chembiochem 3(3 June 2002):490-504. See also special issue of Chemical Reviews 97(1997) and Jeffrey M. Perkel, "Nonribosomal peptide synthesis," The Scientist 17(24 March 2003); http://www.the-scientist.com/yr2003/mar/upfront7_030324.html.

1715. L. Du, B. Shen, "Biosynthesis of hybrid peptide-polyketide natural products," Curr. Opin. Drug Discov. Devel. 4(March 2001):215-228; L. Du, C. Sanchez, B. Shen, "Hybrid peptide-polyketide natural products: biosynthesis and prospects toward engineering novel molecules," Metab. Eng. 3(January 2001):78-95.

1716. R. Lal, R. Kumari, H. Kaur, R. Khanna, N. Dhingra, D. Tuteja, "Regulation and manipulation of the gene clusters encoding type-I PKSs," Trends Biotechnol. 18(June 2000):264-274.

1717. C.R. Hutchinson, R. McDaniel, "Combinatorial biosynthesis in microorganisms as a route to new antimicrobial, antitumor and neuroregenerative drugs," Curr. Opin. Investig. Drugs 2(December 2001):1681-1690; C.R. Hutchinson, "Combinatorial biosynthesis for new drug discovery," Curr. Opin. Microbiol. 1(June 1998):319-329; C.R. Hutchinson, "Drug synthesis by genetically engineered microorganisms," Biotechnology (NY) 12(April 1994):375-380.

1718. J.A. Robinson, "Polyketide synthase complexes: their structure and function in antibiotic biosynthesis," Philos. Trans. R. Soc. Lond. B Biol. Sci. 332(29 May 1991):107-114.

1719. C.R. Hutchinson, I. Fujii, "Polyketide synthase gene manipulation: a structure-function approach in engineering novel antibiotics," Annu. Rev. Microbiol. 49(1995):201-238.

1720. E. Dittmann, B.A. Neilan, T. Borner, "Molecular biology of peptide and polyketide biosynthesis in cyanobacteria," Appl. Microbiol. Biotechnol. 57(November 2001):467-473.

1721. B.S. Moore, C. Hertweck, "Biosynthesis and attachment of novel bacterial polyketide synthase starter units," Nat. Prod. Rep. 19(February 2002):70-99.

1722. J.G. Wallis, J.L. Watts, J. Browse, "Polyunsaturated fatty acid synthesis: what will they think of next?" Trends Biochem. Sci. 27(September 2002):467.

1723. S.J. Sowerby, N.G. Holm, G.B. Petersen, "Origins of life: a route to nanotechnology," Biosystems 61(June 2001):69-78.

1724. J. Otsuka, Y. Nozawa, "Self-reproducing system can behave as Maxwell's demon: theoretical illustration under prebiotic conditions," J. Theor. Biol. 194(1998):205-221.

1725. K. Matsuno, "Compartmentalization of self-reproducing machineries: Multiplication of micro-systems with self-instructing polymerization of amino acids," Origins of Life 10(December 1980):361-370.

1726. C.R. Woese, "On the evolution of cells," Proc. Natl. Acad. Sci. (USA) 99(25 June 2002):8742-8747; http://www.pnas.org/cgi/content/full/99/13/8742.

1727. J.B. Whitfield, "Estimating the age of the polydnavirus/braconid wasp symbiosis," Proc. Natl. Acad. Sci. (USA) 99(28 May 2002):7508-7513.

1728. V. Ahmadjian, "Lichens," Annu. Rev. Microbiol. 19(1965):1-20.

1729. D.C. Smith, "Symbiosis and the biology of lichenised fungi," Symp. Soc. Exp. Biol. 29(1975):373-405.

1730. W.D. Stewart, P. Rowell, A.N. Rai, "Cyanobacteria-eukaryotic plant symbioses," Ann. Microbiol. (Paris) 134B(July-August 1983):205-228.

1731. Thomas H. Nash III, ed., Lichen Biology, Cambridge University Press, New York, 1995.

1732. M.W. Karakashian, "Symbiosis in Paramecium bursaria," Symp. Soc. Exp. Biol. 29(1975):145-173.

1733. Stanley B. Prusiner, "Shattuck lecture — neurodegenerative diseases and prions," New England J. Med. 344(17 May 2001):1516-1526.

1734. Stanley B. Prusiner, "Prions," Proc. Natl. Acad. Sci. (USA) 95(10 November 1998):13363-13383.

1735. R. Riek, S. Hornemann, G. Wider, M. Billeter, R. Glockshuber, K. Wuthrich, "NMR structure of the mouse prion protein domain PrP(121-321)," Nature 382(11 July 1996):180-182. Online prion image source: http://www.mol.biol.ethz.ch/wuthrich/software/molmol/gallery.html.

1736. A. Slepoy, R.R. Singh, F. Pazmandi, R.V. Kulkarni, D.L. Cox, "Statistical mechanics of prion diseases," Phys. Rev. Lett. 87(30 July 2001):58-101.

1737. S. Liemann, R. Glockshuber, "Transmissible spongiform encephalopathies," Biochem. Biophys. Res. Commun. 250(18 September 1998):187-193.

1738. A. Ogayar, M. Sanchez-Perez, "Prions: an evolutionary perspective," Int. Microbiol. 1(September 1998):183-190.

1739. Gudrun Wildegger1, Susanne Liemann, Rudi Glockshuber, "Extremely rapid folding of the C-terminal domain of the prion protein without kinetic intermediates," Nature Struct. Biol. 6(June 1999):550-553; http://www.nature.com/cgi-taf/DynaPage.taf?file=/nsb/journal/v6/n6/full/nsb0699_550.html.

1740. S. Supattapone, H.O. Nguyen, F.E. Cohen, S.B. Prusiner, M.R. Scott, "Elimination of prions by branched polyamines and implications for therapeutics," Proc. Natl. Acad. Sci. (USA) 96(7 December 1999):14529-14534.

1741. B.D. Stollar, T.O. Diener, "Potato spindle tuber viroid. V. Failure of immunological tests to disclose double-stranded RNA or RNA-DNA hybrids," Virology 46(October 1971):168-170; T.O. Diener, "Viroids," Sci. Am. 244(January 1981):66-73; T.O. Diener, "Viroids," Adv. Virus Res. 17(1972):295-313.

1742. D.A. Lafontaine, P. Deschenes, F. Bussiere, V. Poisson, J.P. Perreault, "The viroid and viroid-like RNA database," Nucleic Acids Res. 27(1 January 1999):186-187; http://www.callisto.si.usherb.ca/jpperra.

1743. Ricardo Flores, "A naked plant-specific RNA ten-fold smaller than the smallest known viral RNA: the viroid," C. R. Acad. Sci. III 324(October 2001):943-952.

1744. T.O. Diener, "Viroids and the nature of viroid diseases," Arch. Virol. Suppl. 15(1999):203-220.

1745. Image derived from: Y. Hu, P.A. Feldstein, J. Hammond, R.W. Hammond, P.J. Bottino, R.A. Owens, "Destabilization of potato spindle tuber viroid by mutations in the left terminal loop," J. Gen. Virol. 78(June 1997):1199-1206; online text and image from: Robert A. Owens, "Molecular biology of viroid-host interaction," http://www.barc.usda.gov/psi/mppl/owens/owens2.htm. See also: R.A. Owens, "Viroids," in A. Granoff, R.G. Webster, eds., Encyclopedia of Virology, Second Edition, Academic Press, London, 1999, pp. 1928-1937.

1746. Demin Zhou, "In vitro and in vivo evolution of a synthetic viroid," Schultz Lab Research Projects, Molecular Diversity and Catalytic Antibodies, 14 August 2000; http://schultz.scripps.edu/projects/moleculardiversity/.

1747. T.O. Diener, "Subviral pathogens of plants: viroids and viroidlike satellite RNAs," FASEB J. 5(October 1991):2808-2813.

1748. R.Flores, J.W. Randles, M. Bar-Joseph, T.O. Diener, in M.H.V. van Regenmortel, C. Fauquet, D.H.L. Bishop, E.B. Carstens, M.K. Estes, S.M. Lemon, J. Maniloff, M.A. Mayo, D.J. McGeoch, C.R. Pringle, R.B. Wickner, eds., Virus Taxonomy: Seventh Report of the International Committee on Taxonomy of Viruses, Academic Press, San Diego, CA, 2000, pp. 1009-1024.

1749. Marcos De la Pena, Ricardo Flores, "An extra nucleotide in the consensus catalytic core of a viroid hammerhead ribozyme: implications for the design of more efficient ribozymes," J. Biol. Chem. 276(14 September 2001):34586-34593; http://www.jbc.org/cgi/content/full/276/37/34586.

1750. M. Schmitz, G. Steger, "Description of RNA folding by 'simulated annealing'," J. Mol. Biol. 255(12 January 1996):254-266; A.P. Gultyaev, F.H. van Batenburg, C.W. Pleij, "Dynamic competition between alternative structures in viroid RNAs simulated by an RNA folding algorithm," J. Mol. Biol. 276(13 February 1998):43-55; B.A. Shapiro, D. Bengali, W. Kasprzak, J.C. Wu, "RNA folding pathway functional intermediates: their prediction and analysis," J. Mol. Biol. 312(7 September 2001):27-44.

1751. W.M. Stanley, E.G. Valens, Viruses and the Nature of Life, Dutton, New York, 1961.

1752. Benjamin Harrow, Abraham Mazur, Textbook of Biochemistry, 7th Edition, W.B. Saunders Company, Philadelphia PA, 1958.

1753. Peixuan Guo, C. Zhang, C. Chen, K. Garver, M. Trottier, "Inter-RNA interaction of phage phi29 pRNA to form a hexameric complex for viral DNA transportation," Mol. Cell 2(July 1998):149-155. See also: F. Zhang, S. Lemieux, X. Wu, D. St.-Arnaud, C.T. McMurray, F. Major, D. Anderson, "Function of hexameric RNA in packaging of bacteriophage phi29 DNA in vitro," Mol. Cell 2(July 1998):141-147, 405.

1754. D. Shu, Peixuan Guo, "A viral RNA that binds ATP and contains a motif similar to an ATP-binding aptamer from SELEX," J. Biol. Chem. 278(28 February 2003):7119-7125.

1755. D. Shu, L.P. Huang, S. Hoeprich, P. Guo, "Construction of phi29 DNA-packaging RNA monomers, dimers, and trimers with variable sizes and shapes as potential parts for nanodevices," J. Nanosci. Nanotechnol. 3(August 2003):295-302.

1756. F. d'Herelle, The Bacteriophage: Its Role in Immunity, Williams & Wilkins, Baltimore MD, 1922. Translated by G.H. Smith. See also: F. d'Herelle, The Bacteriophage and Its Clinical Applications, Thomas, Baltimore MD, 1930; A. Raiga-Clemenceau, "d'Herelle's bacteriophage and its therapeutic property," Sem. Hop. Ther. 50(March 1974):229-231. In French.

1757. R.J. Payne, D. Phil, V.A. Jansen, "Phage therapy: the peculiar kinetics of self-replicating pharmaceuticals," Clin. Pharmacol. Ther. 68(September 2000):225-230.

1758. William B. Wood, R.S. Edgar, "Building a bacterial virus," Sci. Amer. 217(July 1967):61-66.

1759. R.S. Edgar, I. Lielausis, "Some steps in the morphogenesis of bacteriophage T4," J. Mol. Biol. 32(March 1968):263-276.

1760. B.F. Poglazov, Morphogenesis of T-Even Bacteriophages, S. Karger, New York, 1973.

1761. Christopher K. Mathews, Elizabeth M. Kutter, Gisela Mosig, Peter B. Berget, Bacteriophage T4, American Society for Microbiology, Washington DC, 1983.

1762. Jim D. Karam, John W. Drake, Kenneth N. Kreuzer, Molecular Biology of Bacteriophage T4, American Society for Microbiology, Washington, DC, 1994.

1763. D.L.D. Caspar, "Movement and self-control in protein assemblies. Quasi-equivalence revisited," Biophys. J. 32(1980):103-135.

1764. V. Zarybnicky, "Mechanism of T-even DNA ejection," J. Theor. Biol. 22(January 1969):33-42.

1765. R. Kilkson, M.F. Maestre, "Structure of T-2 bacteriophage," Nature 195(1962):494-495.

1766. Charles E. Jones, Timothy C. Mueser, Kathleen C. Dudas, Kenneth N. Kreuzer, Nancy G. Nossal, "Bacteriophage T4 gene 41 helicase and gene 59 helicase-loading protein: A versatile couple with roles in replication and recombination," Proc. Natl. Acad. Sci. (USA) 98(17 July 2001):8312-8318; http://www.pnas.org/cgi/content/full/98/15/8312.

1767. W.B. Wood, "Bacteriophage T4 morphogenesis as a model for assembly of subcellular structure," Q. Rev. Biol. 55(December 1980):353-367.

1768. A.D. Doerman, "Lysis and lysis inhibition with *Escherichia coli* bacteriophage," J. Bacteriol. 55(1948):257-275.

1769. R.S. Edgar, R.H. Epstein, "The genetics of a bacterial virus," Sci. Amer. (February 1965).
1770. Alan J. Cann, "Chapter 4: Virus Replication," Principles of Molecular Virology, Third Edition, Academic Press, New York, 2001; http://www.tulane.edu/~dmsander/WWW/224/Replication.html.
1771. Michael T. Madigan, John M. Martinko, Jack Parker, eds., Brock's Biology of Microorganisms, 9th Edition, Prentice-Hall, NJ, 1999; Kenneth J. Ryan, ed., Sherris Medical Microbiology: An Introduction to Infectious Diseases, 3rd Edition, McGraw-Hill, New York, 1994.
1772. H.N. Schulz, T. Brinkhoff, T.G. Ferdelman, M. Hernandez Marine, A. Teske, B.B. Jorgensen, "Dense populations of a giant sulfur bacterium in Namibian shelf sediments," Science 284(16 April 1999):493-495.
1773. E. Olavi Kajander, Neva Ciftcioglu, "Nanobacteria: An alternative mechanism for pathogenic intra- and extracellular calcification and stone formation," Proc. Natl. Acad. Sci. 95(7 July 1998):8274-8279. See also: John Travis, "Nanobacteria strike the kidney again," Science News 155(19 June 1999):395.
1774. H.J. Morowitz, M.E. Tourtellotte, "The smallest living cells," Sci. Amer. 206(March 1962):117-126. See also: Harold J. Morowitz, Mark E. Tourtellotte, "The smallest living cells," in Donald Kennedy, ed., The Living Cell, W.H. Freeman and Co., San Francisco, 1965, pp. 31-39.
1775. F. Mayer, "Principles of functional and structural organization in the bacterial cell: 'Compartments' and their enzymes," FEMA Microbiol. Rev. 10(April 1993):327-345.
1776. Colin R. Bell, Alanna MacGregor, "Chapter 1: The Basics. Microbial Replication," Microbial Ecology Lab, Acadia University, Wolfville, Nova Scotia, August 1996; http://plato.acadiau.ca/courses/biol/Microbiology/Replication.htm.
1777. V. Norris, "Hypothesis: chromosome separation in *Escherichia coli* involves autocatalytic gene expression, transertion and membrane-domain formation," Mol. Microbiol. 16(June 1995):1051-1057.
1778. S.J. Dewar, R. Dorazi, "Control of division gene expression in *Escherichia coli*," FEMS Microbiol. Lett. 187(1 June 2000):1-7.
1779. Jonathan King, "Chapter 9. The biotechnology revolution: self-replicating factories and the ownership of life forms," in Jim Davis, Thomas A. Hirschl, Michael Stack, eds., Cutting Edge: Technology, Information Capitalism and Social Revolution, Verso Books, 1997.
1780. M. Kleerebezemab, P. Hols, J. Hugenholtz, "Lactic acid bacteria as a cell factory: rerouting of carbon metabolism in Lactococcus lactis by metabolic engineering," Enzyme Microb. Technol. 26(1 June 2000):840-848; J. Hugenholtz, M. Kleerebezem, M. Starrenburg, J. Delcour, W. de Vos, P. Hols, "Lactococcus lactis as a cell factory for high-level diacetyl production," Appl. Environ. Microbiol. 66(September 2000):4112-4114; http://aem.asm.org/cgi/content/full/66/9/4112.
1781. Bernard R. Glick, Jack J. Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, American Society for Microbiology, Washington, DC, 2003.
1782. E. Gerhart, H. Wagner, "Replication control in bacterial plasmids," 19 March 1999; http://www.mikrob.slu.se/genexp/general/plasmid.htm. See also: E. Gerhart, H. Wagner, S. Brantl, "Kissing and RNA stability in antisense control of plasmid replication," Trends Biochem. Sci. 23(December 1998):451-454.
1783. C.M. Thomas, "Paradigms of plasmid organization," Mol. Microbiol. 37(August 2000):485-491.
1784. J. Burian, L. Guller, M. Macor, W.W. Kay, "Small cryptic plasmids of multiplasmid, clinical *Escherichia coli*," Plasmid 37(1997):2-14.
1785. B. Futcher, E. Reid, D.A. Hickey, "Maintenance of the 2 micron circle plasmid of *Saccharomyces cerevisiae* by sexual transmission: an example of a selfish DNA," Genetics 118(March 1988):411-415.
1786. D.M. Gordon, "Rate of plasmid transfer among *Escherichia coli* strains isolated from natural populations," J. Gen. Microbiol. 138(January 1992):17-21.
1787. S.G. Sedgwick, S.M. Thomas, V.M. Hughes, D. Lodwick, P. Strike, "Mutagenic DNA repair genes on plasmids from the 'pre-antibiotic era'," Mol. Gen. Genet. 218(August 1989):323-329.
1788. D. Summers, "Timing, self-control and a sense of direction are the secrets of multicopy plasmid stability," Mol. Microbiol. 29(September 1998):1137-1145.
1789. P. Stougaard, S. Molin, K. Nordstrom, "RNAs involved in copy-number control and incompatibility of plasmid R1," Proc. Natl. Acad. Sci (USA) 78(October 1981):6008-6012.
1790. A. Rasooly, R.S. Rasooly, "How rolling circle plasmids control their copy number," Trends Microbiol. 5(November 1997):440-446.
1791. G. del Solar, M. Espinosa, "Plasmid copy number control: an ever-growing story," Mol. Microbiol. 37(August 2000):492-500.
1792. J. Paulsson, M. Ehrenberg, "Noise in a minimal regulatory network: plasmid copy number control," Q. Rev. Biophys. 34(February 2001):1-59.
1793. Gloria del Solar, Rafael Giraldo, Maria Jesus Ruiz-Echevarria, Manuel Espinosa, Ramon Diaz-Orejas, "Replication and control of circular bacterial plasmids," Microbiol. Mol. Biol. Rev. 62(June 1998):434-464; http://mmbr.asm.org/cgi/content/full/62/2/434?view=full&pmid=9618448.
1794. K. Nordstrom, E.G. Wagner, "Kinetic aspects of control of plasmid replication by antisense RNA," Trends Biochem. Sci. 19(July 1994):294-300.
1795. L.E. Bingle, C.M. Thomas, "Regulatory circuits for plasmid survival," Curr. Opin. Microbiol. 4(April 2001):194-200.
1796. D.K. Chattoraj, "Control of plasmid DNA replication by iterons: no longer paradoxical," Mol. Microbiol. 37(August 2000):467-476.
1797. Peter Fantes, Robert Brooks, eds., The Cell Cycle: A Practical Approach, Oxford University Press, New York, 1994.
1798. Christopher Hutchison, David M. Glover, eds., Cell Cycle Control, Oxford University Press, New York, 1995.
1799. B. Stillman, "Cell cycle control of DNA replication," Science 274(6 December 1996):1659-1664.
1800. Gary S. Stein, Renato Baserga, Antonio Giordano, David T. Denhardt, eds., The Molecular Basis of Cell Cycle and Growth Control, Wiley-Liss, New York, 1999.
1801. B.G. den Boer, J.A. Murray, "Triggering the cell cycle in plants," Trends Cell. Biol. 10(June 2000):245-250.
1802. M.J. Farabee, "Cell division: binary fission and mitosis," 2001; http://gened.emc.maricopa.edu/bio/bio181/BIOBK/BioBookmito.html.
1803. M.N. Boddy, P. Russell, "DNA replication checkpoint control," Front. Biosci. 4(1 December 1999):D841-D848; http://www.bioscience.org/1999/v4/d/boddy/fulltext.htm.
1804. I.D. Bowen, M. Bowen, A. Jones, Mitosis and Apoptosis: Matters of Life and Death, Stanley Thomas Pub. Ltd., 1997.
1805. Yvette Petty, "Replication of DNA: How is cellular DNA copied?" Tutorial on DNA Structure, Replication, Transcription, and Protein Synthesis, George Mason University, 1997, http://www.ncc.gmu.edu/dna/replicat.htm. See also animation: Steve Roberson, "DNA Replication," http://www.ncc.gmu.edu/dna/repanim.htm.
1806. Dana M. Krempels, "Plant reproduction, growth and development," Evolution and Biodiversity BIL 160, University of Miami, 2004; http://www.bio.miami.edu/dana/160/160S03_15.html.
1807. S. Pyronnet, N. Sonenberg, "Cell-cycle-dependent translational control," Curr. Opin. Genet. Dev. 11(February 2001):13-18.
1808. P. Gallant, A.M. Fry, E.A. Nigg, "Protein kinases in the control of mitosis: focus on nucleocytoplasmic trafficking," J. Cell Sci. Suppl. 19(1995):21-28.
1809. "The reproduction of cells," Mrs. Washburn's Biology Page, 2000; http://www.geocities.com/auburngirl71/mitosis.htm.
1810. T. Hirano, "Chromosome cohesion, condensation, and separation," Annu. Rev. Biochem. 69(2000):115-144.
1811. R.V. Skibbens, P. Hieter, "Kinetochores and the checkpoint mechanism that monitors for defects in the chromosome segregation machinery," Annu. Rev. Genet. 32(1998):307-337.
1812. K. Wassmann, R. Benezra, "Mitotic checkpoints: from yeast to cancer," Curr. Opin. Genet. Dev. 11(February 2001):83-90.
1813. K.A. Johnson, J.L. Rosenbaum, "Replication of basal bodies and centrioles," Curr. Opin. Cell. Biol. 4(February 1992):80-85.
1814. Y. Ou, J.B. Rattner, "A subset of centrosomal proteins are arranged in a tubular conformation that is reproduced during centrosome duplication," Cell. Motil. Cytoskeleton 47(September 2000):13-24.
1815. R. Balczon, "Centrosome replication in somatic cells: the significance of G1 phase," Curr. Top. Dev. Biol. 49(2000):251-266; "The centrosome in animal cells and its functional homologs in plant and yeast cells," Int. Rev. Cytol. 169(1996):25-82.
1816. K.F. O'Connell, "The centrosome of the early *C. elegans* embryo: inheritance, assembly, replication, and developmental roles," Curr. Top. Dev. Biol. 49(2000):365-384.
1817. E.H. Hinchcliffe, G. Sluder, "'It takes two to tango': understanding how centrosome duplication is regulated throughout the cell cycle," Genes Dev. 15(15 May 2001):1167-1181.

1818. I. Fridovich, “Evidence for the symbiotic origin of mitochondria,” Life Sci. 14(1 March 1974):819-826; L. Margulis, “Symbiotic theory of the origin of eukaryotic organelles: criteria for proof,” Symp. Soc. Exp. Biol. 29(1975):21-38; D. Yang, Y. Oyaizu, H. Oyaizu, G.J. Olsen, C.R. Woese, “Mitochondrial origins,” Proc. Natl. Acad. Sci. (USA) 82(July 1985):4443-4447; M.W. Gray, G. Burger, B.F. Lang, “Mitochondrial evolution,” Science 283(5 March 1999):1476-1481; C.G. Kurland, S.G. Andersson, “Origin and evolution of the mitochondrial proteome,” Microbiol. Mol. Biol. Rev. 64(December 2000):786-820.

1819. S. Douglas, S. Zauner, M. Fraunholz, M. Beaton, S. Penny, L.T. Deng, X. Wu, M. Reith, T. Cavalier-Smith, U.G. Maier, “The highly reduced genome of an enslaved algal nucleus,” Nature 410(26 April 2001):1091-1096, 1040-1041 (comment); P.J. Keeling, J.A. Deane, C. Hink-Schauer, S.E. Douglas, U.G. Maier, G.I. McFadden, “The secondary endosymbiont of the cryptomonad Guillardia theta contains alpha-, beta-, and gamma-tubulin genes,” Mol. Biol. Evol. 16(September 1999):1308-1313; http://mbe.oupjournals.org/cgi/reprint/16/9/1308.pdf.

1820. T. Cavalier-Smith, “The number of symbiotic origins of organelles,” Biosystems 28(1992):91-106, 107-108 (discussion).

1821. “Endosymbiosis and The Origin of Eukaryotes,” 11 October 2003; http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/E/Endosymbiosis.html.

1822. J.M. Archibald, M.B. Rogers, M. Toop, K. Ishida, P.J. Keeling, “Lateral gene transfer and the evolution of plastid-targeted proteins in the secondary plastid-containing alga Bigelowiella natans,” Proc. Natl. Acad. Sci. (USA) 100(24 June 2003):7678-7683, 7419-7420 (comment).

1823. Wayne M. Becker, David W. Deamer, The World of the Cell, Second Edition, Benjamin/Cummings Publishing Company, Redwood City CA, 1991.

1824. T.W. O’Brien, N.D. Denslow, J.C. Anders, B.C. Courtney, “The translation system of mammalian mitochondria,” Biochim. Biophys. Acta 1050(27 August 1990):174-178.

1825. S. Anderson et al, “Sequence and organization of the human mitochondrial genome,” Nature 290(9 April 1981):457-465.

1826. A.M. Kogelnik, M.T. Lott, M.D. Brown, S.B. Navathe, D.C. Wallace, “MITOMAP: An update of the human mitochondrial genome database,” Nucleic Acid Res. 25(January 1997); http://www.gen.emory.edu/mitomap.html.

1827. U. Arnason, “Elephas maximus mitochondrion, complete genome,” NCBI database entry completed on 9 October 2003; http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=17370.

1828. Elaine N. Marieb, Human Anatomy and Physiology, Benjamin/Cummings Publishing Company, Redwood City CA, 1989.

1829. F.K. Gleason, M.P. Ooka, W.P. Cunningham, A.B. Hooper, “Effect of chloramphenicol on replication of mitochondria in Tetrahymena,” J. Cell Physiol. 85(February 1975):59-72.

1830. Z. Baranowski, B. Hrebenda, M. Cieslawska, S.I. Beylina, “Division of Physarum mitochondria during starvation,” Cell Biol. Int. Rep. 15(March 1991):197-204.

1831. Gwen V. Childs, “The mitochondrial life cycle: How do mitochondria replicate?” University of Texas Medical Branch, Galveston, Texas, 19 July 2001; http://cellbio.utmb.edu/cellbio/mitoch2.htm.

1832. S.M. Burgess, M. Delannoy, R.E. Jensen, “MMM1 encodes a mitochondrial outer membrane protein essential for establishing and maintaining the structure of yeast mitochondria,” J. Cell Biol. 126(September 1994):1375-1391.

1833. L.F. Sogo, M.P. Yaffe, “Regulation of mitochondrial morphology and inheritance by Mdm10p, a protein of the mitochondrial outer membrane,” J. Cell Biol. 126(September 1994):1361-1373.

1834. K.H. Berger, L.F. Sogo, M.P. Yaffe, “Mdm12p, a component required for mitochondrial inheritance that is conserved between budding and fission yeast,” J. Cell Biol. 136(10 February 1997):545-553; http://www.jcb.org/cgi/content/full/136/3/545.

1835. G. Schatz, B. Dobberstein, “Common principles of protein translocation across membranes,” Science 271(15 March 1996):1519-1526.

1836. W. Neupert, “Protein import into mitochondria,” Annu. Rev. Biochem. 66(1997):863-917.

1837. P.J. Magalhaes, A.L. Andreu, E.A. Schon, “Evidence for the presence of 5S rRNA in mammalian mitochondria,” Mol. Biol. Cell 9(September 1998):2375-2382; http://www.molbiolcell.org/cgi/content/full/9/9/2375?view=full&pmid=9725900.

1838. Michael Mogie, The Evolution of Asexual Reproduction in Plants, Chapman & Hall, New York, 1992.

1839. M. Cresti, S. Blackmore, J.L. Van Went, Atlas of Sexual Reproduction in Flowering Plants, Springer Verlag, New York, 1992.

1840. B.M. Johri, Reproductive Biology of Plants, Springer Verlag, New York, 2001.

1841. Haig H. Najarian, Sex Lives of Animals Without Backbones, Charles Scribner’s Sons, New York, 1976.

1842. Richard Eliot Blackwelder, The Diversity of Animal Reproduction, CRC Press, 1981.

1843. E.W. Jameson, Vertebrate Reproduction, John Wiley & Sons, New York, 1988.

1844. David Bruce Conn, Atlas of Invertebrate Reproduction and Development, John Wiley & Sons, New York, 1991.

1845. Ernst Knobil, Jimmy D. Neill, eds., Encyclopedia of Reproduction, Academic Press, NY, 1998. (4-volume set).

1846. Barry J. Everitt, Martin H. Johnson, Essential Reproduction, Blackwell Science Inc., New York, 2000.

1847. William H. Masters, Virginia E. Johnson, Robert C. Kolodny, Human Sexuality, 5th Edition, Addison-Wesley Publishing Co., New York, 1995.

1848. Ramon Pinon, Biology of Human Reproduction, University Science Books, 2002.

1849. Brenda Love, Encyclopedia of Unusual Sex Practices, Barricade Books, 1994; http://www.odd-sex.com; Google search, 5 June 2002, on “bizarre sex”: 53,100 entries found.

1850. P. Luksha, “Society as a self-reproducing system,” J. Sociocybernetics 2(2002):13-36; http://www.geocities.com/CapeCanaveral/Hangar/8933/papers/social_SR_e.doc.

1851. Milan Zeleny, ed., Autopoiesis, Dissipative Structures, and Spontaneous Social Orders, AAAS Selected Symposium 55 (AAAS National Annual Meeting, Houston TX, Jan. 3-8, 1979), Westview Press, Boulder, CO, 1980.

1852. Niklas Luhmann, “The autopoiesis of social systems,” in F. Geyer, J. van der Zouwen, eds., Sociocybernetic Paradoxes, Sage, London, 1986; Niklas Luhmann, Social Systems, Stanford University Press, Stanford, CA, 1995. Translated by J. Bednarz.

1853. D.L. Kincaid, “The Convergence Theory of Communication, Self-Organization, and Cultural Evolution,” in D.L. Kincaid, ed., Communication Theory: Eastern and Western Perspectives, Academic Press, San Diego, CA, 1987.

1854. Vincent Kenny, “Steering or drifting? The organization of psychotherapeutic conversation,” in F. Heylighen, E. Rosseel, F. Demeyere, eds., Self-Steering and Cognition in Complex Systems: Toward a New Cybernetics, Gordon Breach Science Publishers, New York, 1990.

1855. Walter J.M. Kickert, “Autopoiesis and the science of (public) administration: essence, sense and nonsense,” Organization Studies 14(1993):261-278.

1856. Klaus Krippendorf, “A second-order cybernetics of otherness,” Systems Research 13(1996):311-328.

1857. Gareth Morgan, Images of Organization, Sage Publications, Thousand Oaks, CA, 1997.

1858. M. Goulian, A. Kornberg, R.L. Sinsheimer, “Enzymatic Synthesis of DNA, Xxiv. Synthesis of Infectious Phage Phi-X174 DNA,” Proc. Natl. Acad. Sci. (USA) 58 (1967):2321-2328.

1859. G.R. Taylor, The Biological Time Bomb, World Publishing Company, New York, 1968.

1860. K.W. Jeon, I.J. Lorch, J.F. Danielli, “Reassembly of living cells from dissociated components,” Science 167(1970):1626-1627.

1861. H.J. Morowitz, “Manufacturing a living organism,” Hospital Practice 9(November 1974):210-215.

1862. J.F. Danielli, “Artificial synthesis of new life forms,” Bull. Atomic Scientists 28(October 1972):20-24.

1863. Richard J. Feldmann, “Applying engineering principles to the design of cellular biology,” Arzneimittelforschung 39(August 1989):1020-1022, 1023 (discussion).

1864. Austin Che, “The next step in bioevolution: Engineering the microbial world,” Dangerous Ideas Seminar, 20 November 2002; http://www.syntheticbiology.org/docs/dangerous_ideas.pdf.

1865. A.R. Mushegian, “The minimal genome concept,” Curr. Opin. Genet. Dev. 9(December 1999):709-714.

1866. A.R. Mushegian, Eugene V. Koonin, “A minimal gene set for cellular life derived by comparison of complete bacterial genomes,” Proc. Natl. Acad. Sci. (USA) 93(1996):10268-10273.

1867. C.M. Fraser, J.D. Gocayne, O. White, M.D. Adams, R.A. Clayton, R.D. Fleischmann, C.J. Bult, A.R. Kerlavage, G. Sutton, J.M. Kelley, L. Fritchman, J.F. Weidman, K.V. Small, M. Sandusky, J. Fuhrmann, D. Nguyen, T.R. Utterback, D.M. Saudek, C.A. Phillips, J.M. Merrick, J.-F. Tomb, B.A. Dougherty, K.F. Bott, P.-C. Hu, T.S. Lucier, S.N. Peterson, H.O. Smith, C.A.I. Hutchinson, J.C. Venter, "The minimal gene complement of *Mycoplasma genitalium*," Science 270(20 October 1995):397-403. See also: "Mycoplasma genitalium, complete genome," http://web.ncbi.nlm.nih.gov:2441/entrez/viewer.fcgi?val=NC_000908.
1868. "Researchers build huge DNA chains," BBC, 27 January 2000; http://www.crystalinks.com/biology5.1.html.
1869. Custom DNA and peptide sequence Web ordering; see:
http://www.perkin-elmer.com:80/ds/230000/dsww0002.html;
http://www.cris.com/~biotech/oligoweb.html;
http://mmr.bmb.colostate.edu/dna/forms/orderDNANet.html;
http://www.genosys.com/text/prods/olg_onl.htm;
http://www.biosyn.com/order.htm; and.
http://mbcf.dfci.harvard.edu/docs/oligoform.html.
1870. H. Koster, H. Blocker, R. Frank, S. Geussenhainer, W. Kaiser, "Total synthesis of a structural gene for the human peptide hormone angiotensin II," Hoppe Seylers Z. Physiol. Chem. 356(October 1975):1585-1593.
1871. M.D. Edge, A.R. Green, G.R. Heathcliffe, P.A. Meacock, W. Schuch, D.B. Scanlon, T.C. Atkinson, C.R. Newton, A.F. Markham, "Total synthesis of a human leukocyte interferon gene," Nature 292(20 August 1981):756-762.
1872. M.A. Wosnick, R.W. Barnett, A.M. Vicentini, H. Erfle, R. Elliott, M. Sumner-Smith, N. Mantei, R.W. Davies, "Rapid construction of large synthetic genes: total chemical synthesis of two different versions of the bovine prochymosin gene," Gene 60(1987):115-127.
1873. R. Jerala, V. Turk, "Regen: program for designing gene assembly," Nucleic Acids Res. 16(11 March 1988):1759-1766.
1874. Z.A. Shabarova, I.N. Merenkova, T.S. Oretskaya, N.I. Sokolova, E.A. Skripkin, E.V. Alexeyeva, A.G. Balakin, A.A. Bogdanov, "Chemical ligation of DNA: the first non-enzymatic assembly of a biologically active gene," Nucleic Acids Res. 19(11 August 1991):4247-4251.
1875. EngeneOS, Inc.; http://www.engeneos.com/.
1876. Robert J. Bradbury, Robiobotics, LLC; Draft Business Plan, September 2001, personal communication to Robert A. Freitas Jr.; http://www.robiobotics.com.
1877. P.L. Luisi, "Toward the engineering of minimal living cells," Anat. Rec. 268(1 November 2002):208-214.
1878. Wetware website; http://model.mit.edu/wetware/.
1879. Justin Gillis, "Scientists planning to make new form of life," Washington Post, Thursday, 21 November 2002, p. A01; http://www.washingtonpost.com/ac2/wp-dyn?pagename=article&node=&contentId=A17496-2002Nov20.
1880. H.O. Smith, C.A. Hutchison 3rd, C. Pfannkoch, J. Craig Venter, "Generating a synthetic genome by whole genome assembly: {phi}X174 bacteriophage from synthetic oligonucleotides," Proc. Natl. Acad. Sci. (USA) 100(23 December 2003):15440-15445. See also: Sylvia Pagán Westphal, "Virus synthesized in a fortnight," NewScientist.com, 14 November 03; http://www.newscientist.com/news/news.jsp?id=ns99994383.
1881. Egea Biosciences, Inc.; http://www.egeabiosciences.com.
1882. Alexandra M. Goho, "Life Made to Order: Efforts to create custom-made organisms — one DNA letter at a time — could yield new sources of energy or novel drugs," Technology Review, April 2003, pp. 50-57. Available on the Internet: www.technnologyreview.com. http://www.technologyreview.com/articles/goho20403.asp?p=1.
1883. "Synthetic Biology: Current Projects," June 2003; http://syntheticbiology.org/projects/.
1884. BioCyc Knowledge Library; http://biocyc.org/.
1885. Jack W. Szostak, David P. Bartel, P. Luigi Luisi, "Synthesizing life," Nature 409(18 January 2001):387-390; http://www.msu.edu/~pennock5/courses/ALife/Nature%20Jan%2001%20Szostak%20Luisi.pdf.
1886. D.P. Bartel, P.J. Unrau, "Constructing an RNA world," Trends Cell Biol. 9(December 1999):M9-M13; D.P. Bartel, in R.E. Gesteland, T.R. Cech, J.E. Atkins, eds., The RNA World, Cold Spring Harbor Laboratory Press, New York, 1999, pp. 143-162.
1887. Per Bro, "Chemical Reaction Automata: Precursors of Synthetic Organisms," talk delivered to the American Chemical Society, Central New Mexico Section, 25 April 1997; see announcement at: http://www.nm.org/~acs/archive/news0497.html.
1888. John Travis, "One small bacterial genome, to go," Science News 155(12 June 1999):377.
1889. Charles Ostman, "Nanobiology — Where Nanotechnology and Biology Come Together," see at: http://www.biota.org/ostman/nchip.htm.
1890. T.M.S. Chang, Artificial Cells, Thomas Books, Springfield, IL, 1972; "Artificial cell biotechnology for medical applications," Blood Purif. 18(2000):91-96.
1891. A.P. Arkin, "Synthetic cell biology," Curr. Opin. Biotechnol. 12(December 2001):638-644.
1892. Una Chen, "Chapter 33. Lymphocyte engineering, its status of art and its future," in Robert P. Lanza, Robert Langer, William L. Chick, eds., Principles of Tissue Engineering, R.G. Landes Company, Georgetown TX, 1997, pp. 527-561.
1893. Thomas F. Knight Jr., Gerald Jay Sussman, "Cellular gate technology," paper presented at Proc. UMC98, First International Conference on Unconventional Models of Computation, Auckland, NZ, January 1998; see also: http://www-swiss.ai.mit.edu/~switz/amorphous/papers/cellgates.ps.gz (postscript version) or http://www-swiss.ai.mit.edu/~switz/amorphous/papers/cellgates (html version).
1894. Tom Knight, "Microbial Engineering Home Page," see at: http://www.ai.mit.edu/people/tk/ce/microbial-engineering.html.
1895. Ron Weiss, George Homsy, Radhika Nagpal, "Programming biological cells," paper presented at the 8th International Conference on Architectural Support for Programming Languages and Operating Systems (ASPLOS '98), Wild and Crazy Ideas Session, San Jose, CA, 1998; see at: http://www-swiss.ai.mit.edu/~rweiss/bio-programming/asplos98-talk.ps, and see abstract at: http://www-swiss.ai.mit.edu/~switz/amorphous/paperlisting.html.
1896. Ron Weiss, George Homsy, Thomas F. Knight, "Toward in vivo digital circuits," paper presented at Dimacs Workshop on Evolution as Computation, Princeton, NJ, January 1999; see at: http://www-swiss.ai.mit.edu/~rweiss/bio-programming/dimacs99-evocomp.ps (postscript version) or http://www-swiss.ai.mit.edu/~rweiss/bio-programming/dimacs99-evocomp-talk(html version), and see abstract at: http://www-swiss.ai.mit.edu/~switz/amorphous/paperlisting.html.
1897. D.H. Pieper, W. Reineke, "Engineering bacteria for bioremediation," Curr. Opin. Biotechnol. 11(June 2000):262-270.
1898. L. Rohlin, M.K. Oh, J.C. Liao, "Microbial pathway engineering for industrial processes: evolution, combinatorial biosynthesis and rational design," Curr. Opin. Microbiol. 4(June 2001):330-335.
1899. T. Murai, M. Ueda, M. Yamamura, H. Atomi, Y. Shibasaki, N. Kamasawa, M. Osumi, T. Amachi, A. Tanaka, "Construction of a starch-utilizing yeast by cell surface engineering," Appl. Environ. Microbiol. 63(April 1997):1362-1366.
1900. E. Saxon, C.R. Bertozzi, "Cell surface engineering by a modified Staudinger reaction," Science 287(17 March 2000):2007-2010.
1901. K.J. Yarema, "New directions in carbohydrate engineering: a metabolic substrate-based approach to modify the cell surface display of sialic acids," Biotechniques 31(August 2001):384-393.
1902. G. Stephanopoulos, "Metabolic engineering," Curr. Opin. Biotechnol. 5(February 1994):196-200.
1903. D.C. Cameron, F.W. Chaplen, "Developments in metabolic engineering," Curr. Opin. Biotechnol. 8(1 April 1997):175-180.
1904. J. Varner, D. Ramkrishna, "Metabolic engineering from a cybernetic perspective. 2. Qualitative investigation of nodal architectures and their response to genetic perturbation," Biotechnol. Prog. 15(May 1999):426-438.
1905. B.N. Kholodenko, H.V. Westerhoff, J. Schwaber, M. Cascante, "Engineering a living cell to desired metabolite concentrations and fluxes: pathways with multifunctional enzymes," Metab. Eng. 2(January 2000):1-13.
1906. R. Verpoorte, R. van der Heijden, J. Memelink, "Engineering the plant cell factory for secondary metabolite production," Transgenic Res. 9(2000):323-43, 321 (discussion).
1907. D.E. Stafford, G. Stephanopoulos, "Metabolic engineering as an integrating platform for strain development," Curr. Opin. Microbiol. 4(June 2001):336-340.
1908. N.P. Minton, M.L. Mauchline, M.J. Lemmon, J.K. Brehm, M. Fox, N.P. Michael, A. Giaccia, J.M. Brown, "Chemotherapeutic tumor targeting using clostridial spores," FEMS Microbiol. Rev. 17(October 1995):357-364.
1909. M.T. Shata, L. Stevceva, S. Agwale, G.K. Lewis, D.M. Hone, "Recent advances with recombinant bacterial vaccine vectors," Mol. Med. Today 6(February 2000):66-71.

1910. B. Drabner, C.A. Guzman, “Elicitation of predictable immune responses by using live bacterial vectors,” Biomol. Eng. 17(March 2001):75-82; E. Medina, C.A. Guzman, “Use of live bacterial vaccine vectors for antigen delivery: potential and limitations,” Vaccine 19(8 February 2001):1573-1580.

1911. A.L. Shiau, Y.L. Chen, C.Y. Liao, Y.S. Huang, C.L. Wu, “Prothymosin alpha enhances protective immune responses induced by oral DNA vaccination against pseudorabies delivered by Salmonella choleraesuis,” Vaccine 19(16 July 2001):3947-3956; A.L. Shiau, C.Y. Chu, W.C. Su, C.L. Wu, “Vaccination with the glycoprotein D gene of pseudorabies virus delivered by nonpathogenic Escherichia coli elicits protective immune responses,” Vaccine 19(30 April 2001):3277-3284.

1912. M. Hense, E. Domann, S. Krusch, P. Wachholz, K.E. Dittmar, M. Rohde, J. Wehland, T. Chakraborty, S. Weiss, “Eukaryotic expression plasmid transfer from the intracellular bacterium Listeria monocytogenes to host cells,” Cell Microbiol. 3(September 2001):599-609; S. Weiss, T. Chakraborty, “Transfer of eukaryotic expression plasmids to mammalian host cells by bacterial carriers,” Curr. Opin. Biotechnol. 12(October 2001):467-472; S. Weiss, S. Krusch, “Bacteria-mediated transfer of eukaryotic expression plasmids into mammalian host cells,” Biol. Chem. 382(April 2001):533-541; A. Darji, S. zur Lage, A.I. Garbe, T. Chakraborty, S. Weiss, “Oral delivery of DNA vaccines using attenuated Salmonella typhimurium as carrier,” FEMS Immunol. Med. Microbiol. 27(April 2000):341-349.

1913. I. Gentschev, G. Dietrich, S. Spreng, S. Pilgrim, J. Stritzker, A. Kolb-Maurer, W. Goebel, “Delivery of protein antigens and DNA by attenuated intracellular bacteria,” Int. J. Med. Microbiol. 291(February 2002):577-582; H. Mollenkopf, G. Dietrich, S.H. Kaufmann, “Intracellular bacteria as targets and carriers for vaccination,” Biol. Chem. 382(April 2001):521-532; G. Dietrich, A. Kolb-Maurer, S. Spreng, M. Schartl, W. Goebel, I. Gentschev, “Gram-positive and Gram-negative bacteria as carrier systems for DNA vaccines,” Vaccine 19(21 March 2001):2506-2512; G. Dietrich, W. Goebel, “DNA vaccine delivery by attenuated intracellular bacteria,” Subcell. Biochem. 33(2000):541-557; G. Dietrich, “Current status and future perspectives of DNA vaccine delivery by attenuated intracellular bacteria,” Arch. Immunol. Ther. Exp. (Warsz) 48(2000):177-182; G. Dietrich, S. Spreng, I. Gentschev, W. Goebel, “Bacterial systems for the delivery of eukaryotic antigen expression vectors,” Antisense Nucleic Acid Drug Dev. 10(October 2000):391-399; I. Gentschev, G. Dietrich, S. Spreng, A. Kolb-Maurer, J. Daniels, J. Hess, S.H. Kaufmann, W. Goebel, “Delivery of protein antigens and DNA by virulence-attenuated strains of Salmonella typhimurium and Listeria monocytogenes,” J. Biotechnol. 83(29 September 2000):19-26; G. Dietrich, A. Bubert, I. Gentschev, Z. Sokolovic, A. Simm, A. Catic, S.H. Kaufmann, J. Hess, A.A. Szalay, W. Goebel, “Delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide Listeria monocytogenes,” Nat. Biotechnol. 16(February 1998):181-5, 138-139 (comment).

1914. S.C. Liu, N.P. Minton, A.J. Giaccia, J.M. Brown, “Anticancer efficacy of systemically delivered anaerobic bacteria as gene therapy vectors targeting tumor hypoxia/necrosis,” Gene Ther. 9(February 2002):291-296; M.J. Lemmon, P. van Zijl, M.E. Fox, M.L. Mauchline, A.J. Giaccia, N.P. Minton, J.M. Brown, “Anaerobic bacteria as a gene delivery system that is controlled by the tumor microenvironment,” Gene Ther. 4(August 1997):791-796; M.E. Fox, M.J. Lemmon, M.L. Mauchline, T.O. Davis, A.J. Giaccia, N.P. Minton, J.M. Brown, “Anaerobic bacteria as a delivery system for cancer gene therapy: in vitro activation of 5-fluorocytosine by genetically engineered clostridia,” Gene Ther. 3(February 1996):173-178, 3(August 1996):741 (erratum).

1915. S. Nuyts, L. Van Mellaert, J. Theys, W. Landuyt, P. Lambin, J. Anne, “Clostridium spores for tumor-specific drug delivery,” Anticancer Drugs 13(February 2002):115-125.

1916. C. Grillot-Courvalin, S. Goussard, P. Courvalin, “Wild-type intracellular bacteria deliver DNA into mammalian cells,” Cell Microbiol. 4(March 2002):177-186; C. Grillot-Courvalin, S. Goussard, P. Courvalin, “Bacteria as gene delivery vectors for mammalian cells,” Curr. Opin. Biotechnol. 10(October 1999):477-481; P. Courvalin, S. Goussard, C. Grillot-Courvalin, “Gene transfer from bacteria to mammalian cells,” C. R. Acad. Sci. III 318(December 1995):1207-1212.

1917. M. Fujimori, J. Amano, S. Taniguchi, “The genus Bifidobacterium for cancer gene therapy,” Curr. Opin. Drug Discov. Devel. 5(March 2002):200-203; K. Yazawa, M. Fujimori, J. Amano, Y. Kano, S. Taniguchi, “Bifidobacterium longum as a delivery system for cancer gene therapy: selective localization and growth in hypoxic tumors,” Cancer Gene Ther. 7(February 2000):269-274.

1918. D. Bermudes, L.M. Zheng, I.C. King, “Live bacteria as anticancer agents and tumor-selective protein delivery vectors,” Curr. Opin. Drug Discov. Devel. 5(March 2002):194-199; X. Luo, Z. Li, S. Lin, T. Le, M. Ittensohn, D. Bermudes, J.D. Runyab, S.Y. Shen, J. Chen, I.C. King, L.M. Zheng, “Antitumor effect of VNP20009, an attenuated Salmonella, in murine tumor models,” Oncol. Res. 12(2001):501-508; J. Tjuvajev, R. Blasberg, X. Luo, L.M. Zheng, I. King, D. Bermudes, “Salmonella-based tumor-targeted cancer therapy: tumor amplified protein expression therapy (TAPET) for diagnostic imaging,” J. Control Release 74(6 July 2001):313-315; D. Bermudes, B. Low, J. Pawelek, “Tumor-targeted Salmonella. Highly selective delivery vectors,” Adv. Exp. Med. Biol. 465(2000):57-63; L.M. Zheng, X. Luo, M. Feng, Z. Li, T. Le, M. Ittensohn, M. Trailsmith, D. Bermudes, S.L. Lin, I.C. King, “Tumor amplified protein expression therapy: Salmonella as a tumor-selective protein delivery vector,” Oncol. Res. 12(2000):127-135; M. Sznol, S.L. Lin, D. Bermudes, L.M. Zheng, I. King, “Use of preferentially replicating bacteria for the treatment of cancer,” J. Clin. Invest. 105(April 2000):1027-1030; http://www.jci.org/cgi/content/full/105/8/1027.

1919. L. Wang, P.G. Schultz, “Expanding the genetic code,” Chem. Commun. (Camb.) (7 January 2002):1-11.

1920. J.W. Chin, S.W. Santoro, A.B. Martin, D.S. King, L. Wang, P.G. Schultz, “Addition of p-azido-L-phenylalanine to the genetic code of Escherichia coli,” J. Am. Chem. Soc. 124(7 August 2002):9026-9027.

1921. J.W. Chin, A.B. Martin, D.S. King, L. Wang, P.G. Schultz, “Addition of a photocrosslinking amino acid to the genetic code of Escherichia coli,” Proc. Natl. Acad. Sci. (USA) 99(20 August 2002):11020-11024; http://www.pnas.org/cgi/content/full/99/17/11020.

1922. L. Wang, A. Brock, B. Herberich, P.G. Schultz, “Expanding the genetic code of Escherichia coli,” Science 292(20 April 2001):498-500, 453-454 (comment).

1923. L. Wang, A. Brock, P.G. Schultz, “Adding L-3-(2-naphthyl)alanine to the genetic code of E. coli,” J. Am. Chem. Soc. 124(6 March 2002):1836-1837.

1924. L. Wang, Z. Zhang, A. Brock, P.G. Schultz, “Addition of the keto functional group to the genetic code of Escherichia coli,” Proc. Natl. Acad. Sci. (USA) 100(7 January 2003):56-61; http://www.pnas.org/cgi/content/full/100/1/56.

1925. Z. Zhang, L. Wang, A. Brock, P.G. Schultz, “The selective incorporation of alkenes into proteins in Escherichia coli,” Angew. Chem. Int. Ed. Engl. 41(2 August 2002):2840-2842.

1926. R.A. Mehl, J.C. Anderson, S.W. Santoro, L. Wang, A.B. Martin, D.S. King, D.M. Horn, P.G. Schultz, “Generation of a bacterium with a 21 amino acid genetic code,” J. Am. Chem. Soc. 125(29 January 2003):935-939. See also: Robert F. Service, “New bug uses strange chemistry,” ScienceNow, 29 January 2003; http://sciencenow.sciencemag.org/cgi/content/full/2003/129/3?etoc.

1927. S.W. Santoro, J.C. Anderson, V. Lakshman, P.G. Schultz, “An archaebacteria-derived glutamyl-tRNA synthetase and tRNA pair for unnatural amino acid mutagenesis of proteins in Escherichia coli,” Nucleic Acids Res. 31(1 December 2003):6700-6709.

1928. Jason W. Chin, T. Ashton Cropp, J. Christopher Anderson, Mridul Mukherji, Zhiwen Zhang, Peter G. Schultz, “An Expanded Eukaryotic Genetic Code,” Science 301(15 August 2003):964-967.

1929. A. Deiters, T.A. Cropp, M. Mukherji, J.W. Chin, J.C. Anderson, P.G. Schultz, “Adding amino acids with novel reactivity to the genetic code of Saccharomyces cerevisiae,” J. Am. Chem. Soc. 125(1 October 2003):11782-11783.

1930. Joseph Jacobson, “Self Replicating Systems,” PowerPoint presentation, 2002; http://cba.media.mit.edu/events/02.10.emergent/jacobson.ppt.

1931. Bede M. Broome, Michael H. Hecht, “Nature disfavors sequences of alternating polar and non-polar amino acids: implications for amyloidogenesis,” J. Mol. Biol. 296(2000):961-968; http://www.princeton.edu/~hecht/pub/jmb00.pdf. See also: Michael H. Hecht, “Research Summary,” 2003; http://www.princeton.edu/~hecht/research.html.

1932. P.M. Burgers, “Eukaryotic DNA polymerases in DNA replication and DNA repair,” Chromosoma 107(September 1998):218-227.

1933. A. Tissier, E.G. Frank, J.P. McDonald, S. Iwai, F. Hanaoka, R. Woodgate, “Misinsertion and bypass of thymine-thymine dimers by human DNA polymerase iota,” EMBO J. 19(2 October 2000):5259-5266; http://emboj.oupjournals.org/cgi/content/full/19/19/5259.

1934. S.S. Parikh, C.D. Mol, D.J. Hosfield, J.A. Tainer, “Envisioning the molecular choreography of DNA base excision repair,” Curr. Opin. Struct. Biol. 9(1999):37-47.

1935. Galina Obmolova, Changill Ban, Peggy Hsieh, Wei Yang, "Crystal structures of mismatch repair protein MutS and its complex with a substrate DNA," Nature 407(12 October 2000):703-710; W. Yang, "Structure and function of mismatch repair proteins," Mutat. Res. 460(2000):245-256.

1936. T.K. Sixma, "DNA mismatch repair: MutS structures bound to mismatches," Curr. Opin. Struct. Biol. 11(2001):47-52.

1937. J. Kyte, R.F. Doolittle, "A simple method for displaying the hydropathic character of a protein," J. Mol. Biol. 157(5 May 1982):105-132.

1938. M.J. Daly, O. Ling, K.W. Minton, "Interplasmidic recombination following irradiation of the radioresistant bacterium Deinococcus radiodurans," J. Bacteriol. 176(December 1994):7506-7515.

1939. K.S. Makarova, L. Aravind, Y.I. Wolf, R.L. Tatusov, K.W. Minton, E.V. Koonin, M.J. Daly, "Genome of the extremely radiation-resistant bacterium Deinococcus radiodurans viewed from the perspective of comparative genomics," Microbiol. Mol. Biol. Rev. 65(March 2001):44-79; http://mmbr.asm.org/cgi/content/full/65/1/44?view=full&pmid=11238985. See also: "The World's Toughest Microbe," Office of Science, U.S. Department of Energy, March 2001; http://www.er.doe.gov/Sub/Accomplishments/Decades_Discovery/76.html.

1940. Michael G. Kaplitt, Arthur D. Loewy, eds., Viral Vectors: Gene Therapy and Neuroscience Applications, Second Edition, Academic Press, New York, 1997.

1941. Angel Cid-Arregui, Alejandro Garcia-Carranca, eds., Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co., 2000.

1942. Curtis A. MacHida, ed., Viral Vectors for Gene Therapy: Methods and Protocols, Humana Press, 2002.

1943. S. El Mehdaoui, A. Touze, S. Laurent, P.Y. Sizaret, D. Rasschaert, P. Coursaget, "Gene transfer using recombinant rabbit hemorrhagic disease virus capsids with genetically modified DNA encapsidation capacity by addition of packaging sequences from the L1 or L2 protein of human papillomavirus type 16," J. Virol. 74(November 2000):10332-10340; http://jvi.asm.org/cgi/content/full/74/22/10332.

1944. D. Endy, L. You, J. Yin, I.J. Molineux, "Computation, prediction, and experimental tests of fitness for bacteriophage T7 mutants with permuted genomes," Proc. Natl. Acad. Sci. (USA) 97(9 May 2000):5375-5380; http://www.pnas.org/cgi/content/full/97/10/5375.

1945. D. Endy, R. Brent, "Modelling cellular behavior," Nature 409(18 January 2001):391-395.

1946. F.W. Studier, "Relationships among different strains of T7 and among T7-related bacteriophages," Virology 95(May 1979):70-84.

1947. J. Yin, "Evolution of bacteriophage T7 in a growing plaque," J. Bacteriol. 175(March 1993):1272-1277.

1948. D. Kong, J. Yin, "Whole-virus vaccine development by continuous culture on a complementing host," Biotechnology (NY) 13(June 1995):583-586.

1949. Jeronimo Cello, Aniko V. Paul, Eckard Wimmer, "Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template," Science 297(9 August 2002):1016-1018, http://www.sciencemag.org/cgi/content/full/1072266/DC1; Robin Orwant, "Scientists build polio virus from scratch," NewScientist.com, 11 July 2002; http://www.newscientist.com/news/news.jsp?id=ns99992539; Andrew Pollack, "Scientists create a live polio virus," The New York Times, 12 July 2002; http://www.nytimes.com/2002/07/12/science/12POLI.html.

1950. D. Enshell-Seijffers, L. Smelyanski, J.M. Gershoni, "The rational design of a 'type 88' genetically stable peptide display vector in the filamentous bacteriophage fd," Nucleic Acids Res. 29(15 May 2001):1-13; http://nar.oupjournals.org/cgi/content/full/29/10/e50 or http://nar.oupjournals.org/cgi/reprint/29/10/e50.pdf.

1951. B. Dietzschold, M.J. Schnell, "New approaches to the development of live attenuated rabies vaccines," Hybrid Hybridomics 21(April 2002):129-134.

1952. K.J. Lee, J.C. de la Torre, "Reverse genetics of arenaviruses," Curr. Top. Microbiol. Immunol. 262(2002):175-193; D.F. Hudson, C. Morrison, S. Ruchaud, W.C. Earnshaw, "Reverse genetics of essential genes in tissue-culture cells: 'dead cells talking'," Trends Cell Biol. 12(June 2002):281-287.

1953. S. Zhao, "A comprehensive BAC resource," Nucleic Acids Res. 29(1 January 2001):141-143.

1954. H. Shizuya, H. Kouros-Mehr, "The development and applications of the bacterial artificial chromosome cloning system," Keio J. Med. 50(March 2001):26-30; H. Shizuya, B. Birren, U.J. Kim, V. Mancino, T. Slepak, Y. Tachiiri, M. Simon, "Cloning and stable maintenance of 300-kilobase-pair fragments of human DNA in *Escherichia coli* using an F-factor-based vector," Proc. Natl. Acad. Sci. (USA) 89(15 September 1992):8794-8797.

1955. P. Giraldo, L. Montoliu, "Size matters: use of YACs, BACs and PACs in transgenic animals," Transgenic Res. 10(April 2001):83-103.

1956. A.W. Higgins, M.G. Schueler, H.F. Willard, "Chromosome engineering: generation of mono- and dicentric isochromosomes in a somatic cell hybrid system," Chromosoma 108(August 1999):256-265.

1957. B. Grimes, H. Cooke, "Engineering mammalian chromosomes," Hum. Mol. Genet. 7(1998):1635-1640.

1958. J.E. Mejia, A. Willmott, E. Levy, W.C. Earnshaw, Z. Larin, "Functional complementation of a genetic deficiency with human artificial chromosomes," Am. J. Hum. Genet. 69(August 2001):315-326.

1959. Steen Rasmussen, Liaohai Chen, Martin Nilsson, Shigeaki Abe, "Bridging nonliving and living matter," Artif. Life 9(Summer 2003):269-316.

1960. J. Shi, D.E. Bergstrom, "Assembly of novel DNA cycles with rigid tetrahedral linkers," Angew. Chem. Int. Ed. Engl. 36(1997):111-113.

1961. Bruce Smith, Markus Krummenacker, "DNA-guided assembly of proteins as a pathway to an assembler," paper presented at the 1997 Albany Conference on Biomolecular Motors and Nanomachines; see abstract at: http://www.wadsworth.org/albcon97/abstract/krummena.htm.

1962. James B. Lewis, Bruce Smith, Markus Krummenacker, "A Proposed Path from Current Biotechnology to a Replicating Assembler," Molecubotics, Inc., November 1996; http://www.molecubotics.com/tech-docs/dgap.html.

1963. Molecubotics, Inc.; http://www.molecubotics.com/info.html.

1964. Bruce Smith, Markus Krummenacker, Jim Lewis, "Constructing a Biotech Assembler: Roadmap and Milestones," Molecubotics, Inc., Version 0.8, 8 November 2000; http://www.molecubotics.com/tech-docs/asm-roadmap-0.7.html. See also: "Biotech as the Fastest Pathway to an Assembler," Molecubotics, Inc., 25 February 2001; http://www.molecubotics.com/tech-docs/biotech-pathway.html.

1965. Gavin D. Meredith, Hayley Wu, Nancy Allbritton, "Novel chemical strategy to link protein to DNA for directed molecular assembly," 11th Foresight Conference on Molecular Nanotechnology, Palo Alto, CA, 9-12 October 2003; http://www.foresight.org/Conferences/MNT11/Abstracts/Meredith/index.html.

1966. E. Braun, Y. Eichen, U. Silvan, G. Ben-Yoseph, "DNA-templated assembly and electrode attachment of a conducting silver wire," Nature 391(19 February 1998):775-778.

1967. J.K.N Mbindyo, B.D. Reiss, B.R. Martin, D.J. Dermody, M.J. Natan, Thomas E. Mallouk, "DNA-directed assembly of gold nanowires on complementary surfaces," Advanced Materials 13(2001):249-254.

1968. Erik Dujardin, Long-Bao Hsin, C.R. Chris Wang, Stephen Mann, "DNA-driven self-assembly of gold nanorods," Chem. Commun. (2001):1264-1265.

1969. John H. Reif, Thomas H. LaBean, Nadrian C. Seeman, "Challenges and applications for self-assembled DNA nanostructures," Proc. Sixth International Workshop on DNA-Based Computers, Leiden, The Netherlands, June 2000, in A. Condon, G. Rozenberg, eds., DIMACS Series in Discrete Mathematics and Theoretical Computer Science, Lecture Notes in Computer Science, Springer-Verlag, Berlin Heidelberg, vol. 2054, 2001, pp. 173-198; http://www.cs.duke.edu/~reif/paper/SELFASSEMBLE/selfassemble.pdf.

1970. B.R. Martin, D.J. Dermody, B.D. Reiss, M. Fang, L.A. Lyon, M.J. Natan, T.E. Mallouk, "Orthogonal self-assembly on colloidal Au-Pt nanorods," Adv. Mater. 11(1999):1021-1025.

1971. Jan Richter, Michael Mertig, Wolfgang Pompe, Ingolf Monch, Hans K. Schackert, "Construction of highly conductive nanowires on a DNA template," Appl. Phys. Lett. 78(22 January 2001):536-538; http://www.biophysik.physik.uni-muenchen.de/staff/PetrasWebpage/pdf-Files/Richter.pdf.

1972. Yu Huang, Xiangfeng Duan, Yi Cui, Lincoln J. Lauhon, Kyoung-Ha Kim, Charles M. Lieber, "Logic gates and computation from assembled nanowire building blocks," Science 294(9 November 2001):1313-1317.

1973. B.D. Reiss, J.K.N. Mbindyo, B.R. Martin, S.R. Nicewarner, T.E. Mallouk, M.J. Natan, C.D. Keating, "DNA-directed assembly of anisotropic nanoparticles on lithographically defined surfaces and in solution," MRS Symp. Proc. 635(2001):C6.2.1-C6.2.6.

1974. Chris Dwyer, Russell Taylor, Richard Superfine, Sean Washburn, Dorothy Erie, "Methodology for the DNA-guided self assembly of novel computing circuitry," paper presented at the 10th Foresight Conference on Molecular Nanotechnology, October 2002; http://www.foresight.org/Conferences/MNT10/Abstracts/Dwyer/index.html (abstract).

1975. John Reif, Hao Yan, Thomas H. LaBean, Liping Feng, "Directed Nucleation Assembly of DNA Tile Complexes for Barcode-Patterned Lattices," Proc. Nat. Acad. Sci. (USA) (23 June 2003); http://www.trnmag.com/Stories/2003/070203/DNA_makes_nano_barcode_070203.html.

1976. Larry W. McLaughlin, Kristen M. Stewart, "Synthesis and Self-Assembly of Metal-Centered DNA Lattices," 11th Foresight Conference on Molecular Nanotechnology, Palo Alto, CA, 9-12 October 2003; http://www.foresight.org/Conferences/MNT11/Abstracts/McLaughlin/index.html.

1977. M.G. Warner, J.E. Hutchison, "Linear assemblies of nanoparticles electrostatically organized on DNA scaffolds," Nat. Mater. 2(April 2003):272-7, 214-215 (comment).

1978. A.P. Alivisatos, K.P. Johnsson, X. Peng, T.E. Wilson, C.J. Loweth, M.P. Bruchez Jr., P.G. Schultz, "Organization of 'nanocrystal molecules' using DNA," Nature 382(15 August 1996):609-611, 581 (comment).

1979. H. Xin, A.T. Woolley, "DNA-templated nanotube localization," J. Am. Chem. Soc. 125(23 July 2003):8710-8711.

1980. A.M Cassell, W.A. Scrivens, J.M. Tour, "Assembly of DNA/fullerene hybrid materials," Angew. Chem. Int. Ed. Engl. 37(1998):1528-1531.

1981. C.A. Mirkin, R.L. Letsinger, R.C. Mucic, J.J.A. Storhoff, "A DNA-based method for rationally assembling nanoparticles into macroscopic materials," Nature 382(15 August 1996):607-609.

1982. C.J. Loweth, W.B. Caldwell, X.G. Peng, A.P. Alivisatos, P.G. Schultz, "DNA-based assembly of gold nanocrystals," Angew. Chem. Intl. Ed. 38(December 1999):1808-1812; http://www3.interscience.wiley.com/cgi-bin/fulltext?ID=62000783&PLACEBO=IE.pdf.

1983. J.M. Perez, T. O'Loughin, F.J. Simeone, R. Weissleder, L. Josephson, "DNA-based magnetic nanoparticle assembly acts as a magnetic relaxation nanoswitch allowing screening of DNA-cleaving agents," J. Am. Chem. Soc. 124(27 March 2002):2856-2857.

1984. Kentaro Tanaka, Atsushi Tengeiji, Tatsuhisa Kato, Namiki Toyama, Mitsuhiko Shionoya, "A discrete self-assembled metal array in artificial DNA," Science 299(21 February 2003):1212-1213.

1985. R. Bashir, "DNA-mediated artificial nanobiostructures: state of the art and future directions," Superlattices Microstruct. 29(January 2001):1-16; http://www.sciencedirect.com/science/article/B6WXB-45BBY69-1J/1/50a5c274d3b5b6f1304e6979de569b8e.

1986. C. Park, J.L Campbell, W.A. Goddard III, "Protein stitchery: Design of a protein for selective binding to a specific DNA sequence," Proc. Natl. Acad. Sci. USA 89(1 October 1992):9094-9096.

1987. Kinneret Keren, Rotem S. Berman, Evgeny Buchstab, Uri Sivan, Erez Braun, "DNA-templated carbon nanotube field-effect transistor," Science 302(21 November 2003):1380-1382, 1310 (comment). See also: "DNA used to create self-assembling nano transistor," ISRAEL21c, 23 November 2003; http://www.israel21c.org/bin/en.jsp?enPage=BlankPage&enDisplay=view&enDispWhat=object&enDispWho=Articles%5el557&enZone=Technology&enVersion=0&.

1988. M. Zheng, A. Jagota, M.S. Strano, A.P. Santos, P. Barone, S.G. Chou, B.A. Diner, M.S. Dresselhaus, R.S. McLean, G.B. Onoa, G.G. Samsonidze, E.D. Semke, M. Usrey, D.J. Walls, "Structure-based carbon nanotube sorting by sequence-dependent DNA assembly," Science 302(28 November 2003):1545-1548. See also: M. Zheng, A. Jagota, E.D. Semke, B.A. Diner, R.S. McLean, S.R. Lustig, R.E. Richardson, N.G. Tassi, "DNA-assisted dispersion and separation of carbon nanotubes," Nat. Mater. 2(May 2003):338-342.

1989. Matthew Cook, Paul W.K. Rothemund, Erik Winfree, "Self-assembled circuit patterns," DNA Computers 9 (http://analytical.chem.wisc.edu/DNA9/), Lecture Notes in Computer Science (LNCS) 2568, 1-4 June 2003; http://www.dna.caltech.edu/Papers/SAcircuits_DNA9.pdf.

1990. S. Xiao, F. Liu, A.E. Rosen, J.F. Hainfeld, N.C. Seeman, K. Musier-Forsyth, Richard A. Kiehl, "Self-assembly of metallic nanoparticle arrays by DNA scaffolding," J. Nanoparticle Res. 4(2002):313-317.

1991. Nadrian C. Seeman, William Goddard, Nagarajan Vaidehi, Erik Winfree, "DNA based nanomechanical devices," NSF NIRT Grant 0103002, NSF Nanoscale Science and Engineering Grantees Conference, 11-13 December 2002; http://www-unix.oit.umass.edu/~nano/NewFiles/Over05_NYU.pdf.

1992. Erik Winfree, "Simulations of computing by self-assembly," 31 May 1998; http://cba.mit.edu/events/03.11.ASE/docs/Winfree.1.pdf.

1993. Thomas H. LaBean, Erik Winfree, John H. Reif, "Experimental progress in computation by self-assembly of DNA tilings," DNA Based Computers 5 (http://psrg.lcs.mit.edu/dna5/), DIMACS 54, 1999, pp. 123-140; http://www.dna.caltech.edu/Papers/LaBeanTX.ps.

1994. Erik Winfree, "Algorithmic self-assembly of DNA: Theoretical motivations and 2-D assembly experiments," J. Biomolecular Struct. Dynam. 11(2000):263-270; http://www.dna.caltech.edu/Papers/algSA_JBSD.pdf.

1995. Erik Winfree, Tony Eng, Grzegorz Rozenberg, "Strong tile models for DNA computing by self-assembly," DNA Based Computers 6 (http://lcnc.nl/dna6/), Lecture Notes in Computer Science (LNCS) 2054, 2001, pp. 63-88; http://www.dna.caltech.edu/Papers/stringtiles.pdf.

1996. Rebecca Schulman, Shaun Lee, Nick Papadakis, Erik Winfree, "One dimensional boundaries for DNA tile self-assembly," DNA Computers 9 (http://analytical.chem.wisc.edu/DNA9/), Lecture Notes in Computer Science (LNCS) 2568, 1-4 June 2003; http://www.dna.caltech.edu/Papers/OneDimBoundaries_DNA9.pdf.

1997. Erik Winfree, Renat Bekbolatov, "Proofreading tile sets: Error correction for algorithmic self-assembly," DNA Computers 9 (http://analytical.chem.wisc.edu/DNA9/), Lecture Notes in Computer Science (LNCS) 2568, 1-4 June 2003; http://www.dna.caltech.edu/Papers/proofreading_DNA9.pdf.

1998. Nadrian C. Seeman, "Structural DNA nanotechnology," paper presented at the 10th Foresight Conference on Molecular Nanotechnology, October 2002; http://www.foresight.org/Conferences/MNT10/Abstracts/Seeman/index.html (abstract).

1999. Nadrian C. Seeman, "DNA nanotechnology: Life's central performer in a new role," The Biological Physicist 2(1 April 2002):2-6; http://www.aps.org/DBP/newsletter/apr02.pdf; Nadrian C. Seeman, "Nanotechnology," Materials Today, January 2003, pp. 24-29; http://www.materialstoday.com/pdfs_6_1/seeman.pdf.

2000. Nadrian C. Seeman, personal communication to Robert A. Freitas Jr., 8 August 2003.

2001. Nadrian C. Seeman, "Synthetic DNA Topology," in Jean-Pierre Sauvage, C. Dietrich-Buchecker, eds., Molecular Catenanes, Rotaxanes and Knots, Wiley-VCH Verlagsgesellschaft Mbh, Weinheim, 1999, pp. 323-356.

2002. J. Fritz, M.K. Baller, H.P. Lang, H. Rothuizen, P. Vettiger, E. Meyer, H.-J. Guntherodt, Ch. Gerber, J.K. Gimzewski, "Translating biomolecular recognition into nanomechanics," Science 288(14 April 2000):316-318; http://www.sciencemag.org/cgi/content/full/288/5464/316.

2003. Guanghua Wu, Haifeng Ji, Karolyn Hansen, Thomas Thundat, Ram Datar, Richard Cote, Michael F. Hagan, Arup K. Chakraborty, Arunava Majumdar, "Origin of nanomechanical cantilever motion generated from biomolecular interactions," Proc. Natl. Acad. Sci. (USA) 98(13 February 2001):1560-1564; http://www.pnas.org/cgi/content/full/98/4/1560.

2004. A. Majumdar, "Bioassays based on molecular nanomechanics," Dis. Markers 18(2002):167-174.

2005. F. Liu, Y. Zhang, Z. Ou-Yang, "Flexoelectric origin of nanomechanic deflection in DNA-microcantilever system," Biosens. Bioelectron. 18(May 2003):655-660.

2006. K.M. Hansen, H.F. Ji, G. Wu, R. Datar, R. Cote, A. Majumdar, T. Thundat, "Cantilever-based optical deflection assay for discrimination of DNA single-nucleotide mismatches," Anal. Chem. 73(1 April 2001):1567-1571.

2007. Guanghua Wu, Ram H. Datar, Karolyn M. Hansen, Thomas Thundat, Richard J. Cote, Arun Majumdar, "Bioassay of prostate-specific antigen (PSA) using microcantilevers," Nat. Biotechnol. 19(1 September 2001):856-860.

2008. R. McKendry, J. Zhang, Y. Arntz, T. Strunz, M. Hegner, H.P. Lang, M.K. Baller, U. Certa, E. Meyer, H.-J. Güntherodt, Ch. Gerber, "Multiple label-free biodetection and quantitative DNA-binding assays on a nanomechanical cantilever array," Proc. Nat. Acad. Sci. (USA) 99(2002):9783-9787; http://monet.physik.unibas.ch/~lang/pub/pnas2002.pdf.

2009. Y. Arntz, J.D. Seelig, H.P. Lang, J. Zhang, P. Hunziker, J.-P. Ramseyer, E. Meyer, M. Hegner, Ch. Gerber, "Label-free protein assay based on a nanomechanical cantilever array ," Nanotechnology 14(2003):86-90; http://monet.physik.unibas.ch/nose/t30119.pdf.

2010. Patrizia Alberti, Jean-Louis Mergny, "DNA duplex-quadruplex exchange as the basis for a nanomolecular machine," Proc. Natl. Acad. Sci. (USA) 100(18 February 2003):1569-1573; http://www.pnas.org/cgi/content/full/100/4/1569.

2011. Jianwei J. Li, Weihong Tan, "A single DNA molecule nanomotor," Nano Letters 2(April 2002):315-318. See also: "Nanomotor Made From Single DNA Molecule Is A First," UniSci News, 16 May 2002; reports at http://unisci.com/stories/20022/0516021.htm and http://www.imm.org/Reports/Rep030.html#DNAmotor.

2012. Bernard Yurke, Andrew J. Turberfield, Allen P. Mills, Jr., Friedrich C. Simmel, Jennifer L. Neumann, "A DNA-fuelled molecular machine made of DNA," Nature 406(10 August 2000):605-608; see also http://www.bell-labs.com/org/physicalsciences/pubs/yurke01.pdf.

2013. Friedrich C. Simmel, Bernard Yurke, "Using DNA to construct and power a nanoactuator," Phys. Rev. E 63(April 2001):041913.

2014. Friedrich C. Simmel, Bernard Yurke, "A DNA-based molecular device switchable between three distinct mechanical states," Appl. Phys. Lett. 80(4 February 2002):883-885; http://www.ee.sc.edu/research/moletronics/teaching/MolecularElectronics2003/Homework_files/homework6_files/groupe2.pdf.

2015. F.C. Simmel, B. Yurke, R.J. Sanyal, "Operation kinetics of a DNA-based molecular switch," J. Nanosci. Nanotech. 2(June-August 2002):383-390.

2016. Andrew J. Turberfield, J.C. Mitchell, Bernard Yurke, Allen P. Mills Jr., M.I. Blakey, Friedrich C. Simmel, "DNA fuel for free-running nanomachines," Phys. Rev. Lett. 90(21 March 2003):118102.

2017. R.C. Merkle, "Biotechnology as a route to nanotechnology," Trends in Biotechnology 17(July 1999):271-274; http://www.merkle.com/papers/bionano.html.

2018. L. Feng, S.H. Park, J.H. Reif, H. Yan, "A two-state DNA lattice switched by DNA nanoactuator," Angew. Chem. Intl. Ed. 42(2003):4342-4346.

2019. Hao Yan, Sung Ha Park, Gleb Finkelstein, John H. Reif, Thomas H. LaBean, "DNA-templated self-assembly of protein arrays and highly conductive nanowires," Science 301 (26 September 2003):1882-1884; http://www.sciencemag.org/cgi/content/short/301/5641/1882. See also: Kimberly Patch, "DNA forms nano waffles," Technology Research News, 22/29 October 2003; http://www.trnmag.com/Stories/2003/102203/DNA_forms_nano_waffles_102203.html.

2020. Hao Yan, Thomas H. LaBean, Liping Feng, John H. Reif, "Directed nucleation assembly of DNA tile complexes for barcode-patterned lattices," Proc. Natl. Acad. Sci. (USA) 100(2003):8103.

2021. Richard T. Pomerantz, Michael Anikin, Jordanka Zlatanova, William T. McAllister, "RNA Polymerase as an Information-Dependent Molecular Motor," 11th Foresight Conference on Molecular Nanotechnology, Palo Alto, CA, 9-12 October 2003; http://www.foresight.org/Conferences/MNT11/Abstracts/Pomerantz/index.html.

2022. John H. Reif, "The design of autonomous DNA nanomechanical devices: walking and rolling DNA," The 8th International Meeting on DNA Based Computers (DNA 8), Sapporo, Japan, 10-13 June 2002, Lecture Notes in Computer Science, New York, 2002; to appear in Natural Computing, DNA8 special issue, 2003.; http://www.cs.duke.edu/~reif/paper/DNAmotor/DNAmotor.pdf.

2023. Liping Feng, Sung Ha Park, Yan Liu, Yan Liu, John H. Reif, Hao Yan, "A two state DNA lattice actuated by DNA motors," submitted for publication, 2003; http://www.cs.duke.edu/~reif/vita/topics/biomolecular.html.

2024. Wolfgang Fritzsche, "DNA-based molecular construction," International Workshop, 23-25 May 2002, Jena, Germany, Institute for Physical High Technology; http://www.ipht-jena.de/BEREICH_3/molnano/DNA2002/pdf/program.pdf.

2025. C.A. Mirkin, "Programming the assembly of two- and three-dimensional architectures with DNA and nanoscale inorganic building blocks," Inorg. Chem. 39(2000):2258; http://pubs.acs.org/CHECKCCIP-998779135/isubscribe/journals/inocaj/jtext.cgi?inocaj/39/i11/html/ic991123r.html.

2026. Robert F. Service, "Nanotechnology: Biology Offers Nanotechs a Helping Hand," 20 December 2002; http://www.sciencemag.org/cgi/content/full/298/5602/2322?etoc.

2027. Steven A. Benner, et al, "Redesigning nucleic acids," Pure Appl. Chem. 70(1998):263-266.

2028. S. Nakashima, N. Matsuura, F. Nagatsugi, M. Maeda, S. Sasaki, "Synthesis and evaluation of oligonucleotides incorporating novel artificial nucleobases for the selective formation of non-natural type triplexes," Nucleic Acids Symp. Ser. 37(1997):33-34.

2029. M. Berger, S.D. Luzzi, A.A. Henry, Floyd E. Romesberg, "Stability and selectivity of unnatural DNA with five-membered-ring nucleobase analogues," J. Am. Chem. Soc. 124(20 February 2002):1222-1226.

2030. S. Obika, Y. Hari, M. Sekiguchi, T. Imanishi, "Stable oligonucleotide-directed triplex formation at target sites with CG interruptions: strong sequence-specific recognition by 2',4'-bridged nucleic-acid-containing 2-pyridones under physiological conditions," Chemistry 8(18 October 2002):4796-4802.

2031. T. Kanai, M. Ichino, T. Kojima, "Pyrimidine nucleosides. II. The synthesis of unnatural pyrimidine nucleosides saturated at 5,6-double bond," Chem. Pharm. Bull. (Tokyo) 17(April 1969):650-652.

2032. T. Fujiwara, M. Kimoto, H. Sugiyama, I. Hirao, S. Yokoyama, "Synthesis of 6-(2-thienyl)purine nucleoside derivatives that form unnatural base pairs with pyridin-2-one nucleosides," Bioorg. Med. Chem. Lett. 11(20 August 2001):2221-2223.

2033. Y. Wu, M. Fa, E.L. Tae, P.G. Schultz, Floyd E. Romesberg, "Enzymatic phosphorylation of unnatural nucleosides," J. Am. Chem. Soc. 124(11 December 2002):14626-14630.

2034. Markus Berger, Yiqin Wu, Anthony K. Ogawa, Dustin L. McMinn, Peter G. Schultz, Floyd E. Romesberg, "Universal bases for hybridization, replication and chain termination," Nucleic Acids Res. 28(1 August 2000):2911-2914; http://nar.oupjournals.org/cgi/content/full/28/15/2911.

2035. D. Loakes, "Survey and summary: The applications of universal DNA base analogues," Nucleic Acids Res. 29(15 June 2001):2437-2447.

2036. A.J. Tackett, P.D. Morris, R. Dennis, T.E. Goodwin, K.D. Raney, "Unwinding of unnatural substrates by a DNA helicase," Biochemistry 40(16 January 2001):543-548.

2037. P.E. Nielsen, M. Egholm, "An introduction to peptide nucleic acid," Curr. Issues Mol. Biol. 1(1999):89-104; P.E. Nielsen, "Targeting double stranded DNA with peptide nucleic acid (PNA)," Curr. Med. Chem. 8(April 2001):545-550.

2038. P. Garner, B. Sherry, S. Moilanen, Y. Huang, "In vitro stability of alpha-helical peptide nucleic acids (alphaPNAs)," Bioorg. Med. Chem. Lett. 11(3 September 2001):2315-2317.

2039. J.C. Chaput, J.K. Ichida, J.W. Szostak, "DNA polymerase-mediated DNA synthesis on a TNA template," J. Am. Chem. Soc. 125(29 January 2003):856-857. See also: Philip Ball, "DNA look-alike fools enzyme: Artificial molecule acts as template for DNA," Nature ScienceUpdate, 4 February 2003; http://www.nature.com/nsu/030203/030203-1.html.

2040. C.Y. Switzer, S.E. Moroney, Steven A. Benner, "Enzymatic incorporation of a new base pair into DNA, and RNA," J. Am. Chem. Soc. 111(1989):8322-8323.

2041. J.A. Piccirilli, T. Krauch, S.E. Moroney, Steven A. Benner, "Enzymatic incorporation of a new base pair into DNA and RNA extends the genetic alphabet," Nature 343(1990):33-37.

2042. E. Szathmary, "What is the optimum size for the genetic alphabet?" Proc. Natl. Acad. Sci. (USA) 89(1992):2614-2618.

2043. M.J. Lutz, H.A. Held, M. Hottiger, U. Hübscher, Steven A. Benner, "Differential discrimination of DNA polymerases for variants of the non-standard nucleobase pair between xanthosine, and 2,4-diaminopyrimidine, two components of an expanded genetic alphabet," Nucl. Acids Res. 24(1996):1308-1313.

2044. D.A. MacDonaill, "Tautomerism as a constraint on the composition of alternative nucleotide alphabets," in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 106-110; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub3188.pdf.

2045. Robert J. Bradbury, "Protein based assembly of nanoscale parts," Aeiveos Corp., September 2001, http://www.aeiveos.com/~bradbury/Papers/PBAoNP.html.

2046. Andreas Holzenburg, Nigel S. Scrutton, "Enzyme-catalyzed electron and radical transfer," Subcellular Biochemistry, Vol. 35, Plenum Publ. Corp, New York, 2000.

2047. Robert A. Freitas Jr., "A novel pathway to first-generation molecular assemblers," Aeiveos Corp., 18 November 1998; http://www.aeiveos.com/~bradbury/Papers/ANPtFGMA.html; "Mechanoenzymes: A non-SPM-based approach to molecular mechanoassembly," privately circulated document, 21 February 2000; http://www.aeiveos.com/~bradbury/Authors/Engineering/Freitas-RA/MAnSPMBAtMM.html.

2048. Tom R. Craver, "Softening the blow," Nanotechnology Magazine Pre-Press 2(April 1996):9-11.

2049. Patrick Cramer, David A. Bushnell, Roger D. Kornberg, "Structural basis of transcription: RNA polymerase II at 2.8 Angstrom resolution," Science 292(8 June 2001):1863-1876; Averell L. Gnatt, Patrick Cramer, Jianhua Fu, David A. Bushnell, Roger D. Kornberg, "Structural basis of transcription: An RNA polymerase II elongation complex at 3.3 A resolution," Science 292(8 June 2001):1876-1882, 1844-1846 (comment); Science 292(20 April 2001):411-414 (comment).

2050. P.A. Lohse, J.W. Szostak, "Ribozyme-catalyzed amino-acid transfer reactions," Nature 381(30 May 1996):442-444.

2051. A.J. Hager, J.D. Pollard, J.W. Szostak, "Ribozymes: aiming at RNA replication and protein synthesis," Chem. Biol. 3(September 1996):717-725.

2052. G.A. Soukup, R.R. Breaker, "Nucleic acid molecular switches," Trends Biotechnol. 17(December 1999):469-476.

2053. M. Warashina, T. Kuwabara, K. Taira, "Working at the cutting edge: the creation of allosteric ribozymes," Structure Fold Des. 8(15 November 2000):R207-R212; T. Kuwabara, M. Warashina, K. Taira, "Allosterically controllable ribozymes with biosensor functions," Curr. Opin. Chem. Biol. 4(December 2000):669-677.

2054. Wendy K. Johnston, Peter J. Unrau, Michael S. Lawrence, Margaret E. Glasner, David P. Bartel, "RNA-catalyzed RNA polymerization: accurate and general RNA-templated primer extension," Science 292(18 May 2001):1319-1325, 1278 (comment).

2055. L. Masip, J.L. Pan, S. Haldar, J.E. Penner-Hahn, M.P. DeLisa, G. Georgiou, J.C. Bardwell, J.F. Collet, "An engineered pathway for the formation of protein disulfide bonds," Science 303(20 February 2004):1185-1189. See also: "Evolution Caught In The Act," Science Daily, 20 February 2004; http://www.sciencedaily.com/releases/2004/02/040220074308.htm.

2056. Manfred Schliwa, Günther Woehlke, "Molecular motors," Nature 422(17 April 2003):759-765; http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v422/n6933/full/nature01601_fs.html.

2057. Thomas Scheibel, Raghuveer Parthasarathy, George Sawicki, Xiao-Min Lin, Heinrich Jaeger, Susan Lindquist, "Conducting nanowires built by controlled self-assembly of amyloid fibers and selective metal deposition," Proc. Natl. Acad. Sci. (USA) 100(15 April 2003):4527-4532. See also: http://www.wi.mit.edu/nap/features/nap_feature_nanowire2.html.

2058. Meital Reches, Ehud Gazit, "Casting metal nanowires within discrete self-assembled peptide nanotubes," Science 300(25 April 2003):625-627; http://www.sciencemag.org/cgi/content/full/300/5619/625.

2059. P.M. Okamoto, B. Tripet, J. Litowski, R.S. Hodges, R.B. Vallee, "Multiple distinct coiled-coils are involved in dynamin self-assembly," J. Biol. Chem. 274(9 April 1999):10277-10286.

2060. J.E. Hinshaw, "Dynamin spirals," Curr. Opin. Struct. Biol. 9(April 1999):260-267.

2061. M.H. Stowell, B. Marks, P. Wigge, H.T. McMahon, "Nucleotide-dependent conformational changes in dynamin: evidence for a mechanochemical molecular spring," Nat. Cell Biol. 1(May 1999):27-32.

2062. J.E. Hinshaw, "Dynamin and its role in membrane fission," Annu. Rev. Cell Dev. Biol. 16(2000):483-519.

2063. M.A. McNiven, H. Cao, K.R. Pitts, Y. Yoon, "The dynamin family of mechanoenzymes: pinching in new places," Trends Biochem. Sci. 25(March 2000):115-120.

2064. K. Lu, J. Jacob, P. Thiyagarajan, V.P. Conticello, D.G. Lynn, "Exploiting amyloid fibril lamination for nanotube self-assembly," J. Am. Chem. Soc. 125(28 May 2003):6391-6393.

2065. G.R. Dieckmann, A.B. Dalton, P.A. Johnson, J. Razal, J. Chen, G.M. Giordano, E. Munoz, I.H. Musselman, R.H. Baughman, R.K. Draper, "Controlled assembly of carbon nanotubes by designed amphiphilic peptide helices," J. Am. Chem. Soc. 125(19 February 2003):1770-1777.

2066. Jeffrey D. Hartgerink, Elia Beniash, Samuel I. Stupp, "Self-assembly and mineralization of peptide-amphiphile nanofibers," Science 294(23 November 2001):1684-1688, 1635-1637 (comment); http://www.sciencemag.org/cgi/content/abstract/294/5547/1684; Jeffrey D. Hartgerink, Elia Beniash, Samuel I. Stupp, "Peptide-amphiphile nanofibers: A versatile scaffold for the preparation of self-assembling materials," Proc. Natl. Acad. Sci. (USA) 99(16 April 2002):5133-5138; http://www.pnas.org/cgi/content/full/99/8/5133.

2067. H. Chen, M. Banaszak Holl, B.G. Orr, L. Majoros, B.H. Clarkson, "Interaction of dendrimers (artificial proteins) with biological hydroxyapatite crystals," J. Dent. Res. 82(2003):443-448; http://jdr.iadrjournals.org/cgi/content/full/82/6/443.

2068. I.A. Banerjee, L. Yu, H. Matsui, "Cu nanocrystal growth on peptide nanotubes by biomineralization: Size control of Cu nanocrystals by tuning peptide conformation," Proc. Natl. Acad. Sci. (USA) 100(2003):14678-14682; http://www.pnas.org/cgi/content/full/100/25/14678.

2069. Steven S. Smith, "A self-assembling nanoscale camshaft: Implications for nanoscale materials and devices constructed from proteins and nucleic acids," Nano Lett. 1(2001):51-56.

2070. G.D. Bachand, C.D. Montemagno, "Constructing organic/inorganic NEMS devices powered by bio-molecular motors," Biomedical Microdevices 2(2000):179-184.

2071. C.D. Montemagno, G.D. Bachand, "Constructing nanomechanical devices powered by biomolecular motors," Nanotechnology 10(September 1999):225-231; Carlo D. Montemagno, George D. Bachand, Scott J. Stelick, Marlene Bachand, "Constructing biological motor powered nanomechanical devices," 6th Foresight Conference on Molecular Nanotechnology, November 1998; http://www.foresight.org/Conferences/MNT6/Papers/Montemagno/index.html.

2072. R.K. Soong, G.D. Bachand, H.P. Neves, A.G. Olkhovets, H.G. Craighead, C.D. Montemagno, "Powering an inorganic nanodevice with a biomolecular motor," Science 290(24 November 2000):1555-1558; R.K. Soong, S.J. Stelick, G.D. Bachand, C.D. Montemagno, "Evaluating adhesion strength of biological molecules to nanofabricated substrates," Technical Proceedings of the Second Conference on Modeling and Simulation of Microsystems, 1999 Conference, Puerto Rico, 1999.

2073. Haiqing Liu, Jacob J. Schmidt, George D. Bachand, Shahir S. Rizk, Loren L. Looger, Homme W. Hellinga, Carlo D. Montemagno, "Control of a biomolecular motor-powered nanodevice with an engineered chemical switch," Nat. Mater. 1(November 2002):173-177.

2074. Werner Kliche, Setsuko Fujita-Becker, Martin Kollmar, Dietmar J. Manstein, F. Jon Kull, "Structure of a genetically engineered molecular motor," EMBO J. 20(15 January 2001):40-46; http://emboj.oupjournals.org/cgi/content/full/20/1/40.

2075. R. Andrew McMillan, Chad D. Paavola, Jeanie Howard, Suzanne L. Chan, Nestor J. Zaluzec, Jonathan D. Trent, "Ordered nanoparticle arrays formed on engineered chaperonin protein templates," Nat. Mater. 1(December 2002):247-252. See also: http://amesnews.arc.nasa.gov/releases/2002/02_122AR.html and http://amesnews.arc.nasa.gov/releases/2002/02images/bionano/bionano.html.

2076. N. Kessler, D. Perl-Treves, L. Addadi, "Monoclonal antibodies that specifically recognize crystals of dinitrobenzene," FASEB J. 10(October 1996):1435-1442.

2077. M. Kam, D. Perl-Treves, R. Sfez, L. Addadi, "Specificity in the recognition of crystals by antibodies" J. Mol. Recognit. 7(December 1994):257-264; M. Kam, D. Perl-Treves, D. Caspi, L. Addadi, "Antibodies against crystals," FASEB J. 6(May 1992):2608-2613.

2078. P. Hasselbacher, H.R. Schumacher, "Immunoglobulin in tophi and on the surface of monosodium urate crystals," Arthritis Rheum. 21(April 1978):353-361; P. Hasselbacher, "Binding of IgG and complement protein by monosodium urate monohydrate and other crystals," J. Lab. Clin. Med. 94(October 1979):532-541; F. Kozin, D.J. McCarty, "Molecular orientation of immunoglobulin G adsorbed to microcrystalline monosodium urate monohydrate," J. Lab. Clin. Med. 95(January 1980):49-58; T. Bardin, P. Varghese Cherian, H.R. Schumacher, "Immunoglobulins on the surface of monosodium urate crystals: an immunoelectron microscopic study," J. Rheumatol. 11(June 1984):339-341.

2079. J.M. Verdier, K.V. Ewart, M. Griffith, C.L. Hew, "An immune response to ice crystals in North Atlantic fishes," Eur. J. Biochem. 241(1 November 1996):740-743.

2080. M. Gross, "Molecular recognition. Crystallographic antibodies," Nature 373(12 January 1995):105-106.

2081. D. Perl-Treves, N. Kessler, D. Izhaky, L. Addadi, "Monoclonal antibody recognition of cholesterol monohydrate crystal faces," Chem. Biol. 3(July 1996):567-577.

2082. N. Busch, F. Lammert, S. Matern, "Biliary secretory immunoglobulin A is a major constituent of the new group of cholesterol crystal-binding proteins," Gastroenterology 115(July 1998):129-138; D. Izhaky, L. Addadi, "Stereoselective interactions of a specialized antibody with cholesterol and epicholesterol monolayers," Chemistry 6(3 March 2000):869-874; M. Geva, D. Izhaky, D.E. Mickus, S.D. Rychnovsky, L. Addadi, "Stereoselective recognition of monolayers of cholesterol, ent-cholesterol, and epicholesterol by an antibody," Chembiochem. 2(1 April 2001):265-271; F. Lammert, S. Sudfeld, N. Busch, S. Matern, "Cholesterol crystal binding of biliary immunoglobulin A: visualization by fluorescence light microscopy," World J. Gastroenterol. 7(April 2001):198-202; M. Epple, P. Lanzer, "How much interdisciplinarity is required to understand vascular calcifications? Formulation of four basic principles of vascular calcification," Z. Kardiol. 90(2001):2-5 (Suppl 3).

2083. J.J. Mond, A. Lees, C.M. Snapper, "T cell-independent antigens type 2," Annu. Rev. Immunol. 13(1995):655-692.

2084. D.A. Walters, B.L. Smith, A.M. Belcher, G.T. Paloczi, G.D. Stucky, D.E. Morse, P.K. Hansma, "Modification of calcite crystal growth by abalone shell proteins: an atomic force microscope study," Biophys. J. 72(March 1997):1425-1433.

2085. J.B. Thompson, G.T. Paloczi, J.H. Kindt, M. Michenfelder, B.L. Smith, G. Stucky, D.E. Morse, P.K. Hansma, "Direct observation of the transition from calcite to aragonite growth as induced by abalone shell proteins," Biophys. J. 79(December 2000):3307-3312; http://www.biophysj.org/cgi/content/full/79/6/3307.

2086. S. Brown, M. Sarikaya, E. Johnson, "A genetic analysis of crystal growth," J. Mol. Biol. 299(9 June 2000):725-735; S. Brown, "Metal-recognition by repeating polypeptides," Nat. Biotechnol. 15(March 1997):269-272. See also: Rosemary Braun, Klaus Schulten, Dan Heidel, Mehmet Sarikaya, "Molecular Dynamics Study of Inorganic Surface Recognition by Engineered Proteins," 8th Foresight Conference on Molecular Nanotechnology, November 2000; http://www.foresight.org/Conferences/MNT8/Abstracts/Goddard/index.html.

2087. C.F. Verkoelen, B.G. Van Der Boom, J.C. Romijn, "Identification of hyaluronan as a crystal-binding molecule at the surface of migrating and proliferating MDCK cells," Kidney Int. 58(September 2000):1045-1054. See also: C.F. Verkoelen, B.G. van der Boom, A.B. Houtsmuller, F.H. Schroder, J.C. Romijn, "Increased calcium oxalate monohydrate crystal binding to injured renal tubular epithelial cells in culture," Am. J. Physiol. 274(May 1998):F958-F965; http://ajprenal.physiology.org/cgi/content/full/274/5/F958.

2088. N. Kessler, D. Perl-Treves, L. Addadi, M. Eisenstein, "Structural and chemical complementarity between antibodies and the crystal surfaces they recognize," Proteins 34(15 February 1999):383-394.

2089. B.X. Chen, S.R. Wilson, M. Das, D.J. Coughlin, B.F. Erlanger, "Antigenicity of fullerenes: antibodies specific for fullerenes and their characteristics," Proc. Natl. Acad. Sci. (USA) 95(1 September 1998):10809-10813.

2090. David Izhaky, Israel Pecht, "What else can the immune system recognize?" Proc. Natl. Acad. Sci. (USA) 95(29 September 1998):11509-11510.

2091. B.C. Braden, B.F. Erlanger, B.-X. Kirschner, S.R. Wilson, "Monoclonal antibodies to fullerenes," in N. Martin, M. Maggini, D.M. Guldi, eds., Fullerenes 2000, Volume 9: Functionalized Fullerenes, The Electrochemical Society, Spring 2000, pp. 233-239.

2092. "Anti C60 Fullerene antibody," Bioactive Fullerenes Research Group, Center for Advanced Materials and nanotechnology, New York University; http://www.nyu.edu/projects/nanotechnology/c60/c60.htm.

2093. B.C. Braden, F.A. Goldbaum, B.X. Chen. A.N. Kirschner, S.R. Wilson, B.F. Erlanger, "X-ray crystal structure of an anti-buckminsterfullerene antibody fab fragment: biomolecular recognition of C60," Proc. Natl. Acad. Sci. (USA) 97(24 October 2000):12193-12197; http://www.pnas.org/cgi/content/full/97/22/12193.

2094. Stephen R. Wilson, Austin N. Kirschner, Bernard F. Erlanger, Bradford C. Braden, presentation at NanoSpace 2000, reported by R. Dagani, "NASA Goes Nano," Chem. Eng. News 78(28 February 2000):39-42. See also: http://www.nyu.edu/projects/nanotechnology/nanotube/nanotube.htm.

2095. Stephen R. Wilson, Bernard Erlanger, Bradford Braden, Austin N. Kirschner, "Fullerene Nanotools from Biology," 9th Foresight Conference on Molecular Nanotechnology, November 2001; http://www.foresight.org/Conferences/MNT9/Abstracts/Wilson/index.html. See also: Bernard F. Erlanger, "Recognition of Single Wall Carbon Nanotubes by an Anti-Fullerene Antibody," Nanotech and Biotech Convergence-2002, 6-7 May 2000, Stamford, CT, May 7th Session; http://www.bccresearch.com/nanobio2002/.

2096. "Carbon nanotube antibody," Carbon Nanotube Research Group, Center for Advanced Materials and nanotechnology, New York University; http://www.nyu.edu/projects/nanotechnology/nanotube/nanotube.htm.

2097. William A. Goddard, III, Nagarajan Vaidehi, Wely Floriano, Brian Palmer, Changmoon Park, Deepshika Datta, " Bionanotechnology — de novo simulations and design," lecture at the 8th Foresight Conference on Molecular Nanotechnology, November 2000; http://www.foresight.org/Conferences/MNT8/Abstracts/Goddard/index.html.

2098. Andreas Skiebe, Andreas Hirsch, Holger Klos, Bernd Gotschy, "[DBU]C$_{60}$. Spin pairing in a fullerene salt," Chem. Phys. Lett. 220(1994):138-140.

2099. Ramakrishnan Subramanian, Pierre Boulas, M.N. Vijayshee, Francis D'Souzaj, M. Thomas Jones, Karl M. Kadish, "A Facile and Selective Method for the Solution-phase Generation of C_{60}^{-} and C_{60}^{-2}," J. Chem. Soc. Chem. Commun. (1994):1847-1848.

2100. Vincenzo Balzani, Alberto Credi, Margherita Venturi, Molecular Devices and Machines: A Journey into the Nanoworld, VCH Verlagsgesellschaft MBH, 2003.

2101. Karen Hopkin, "Designer genomes," Scientific American Presents: Extreme Engineering 10(Winter 1999):78-81.

2102. Tanja Klaus, R. Joerger, E. Olsson, C.G. Granqvist, "Silver-based crystalline nanoparticles, microbially fabricated," Proc. Natl. Acad. Sci. (USA) 96(23 November 1999):13611-13614; Proc. Natl. Acad. Sci. (USA) 96(7 December 1999):14183-14185 (comment); "Bacteria with a silver lining," BBC Online, 23 November 1999; http://news.bbc.co.uk/hi/english/sci/tech/newsid_533000/533416.stm.

2103. T. Klaus-Joerger, R. Joerger, E. Olsson, C. Granqvist, "Bacteria as workers in the living factory: metal-accumulating bacteria and their potential for materials science," Trends Biotechnol. 19(January 2001):15-20.

2104. Ronald S. Oremland, Mitchell J. Herbel, Jodi Switzer Blum, Sean Langley, Terry J. Beveridge, Pulickel M. Ajayan, Thomas Sutto, Amanda V. Ellis, Seamus Curran, "Structural and spectral features of selenium nanospheres produced by Se-respiring bacteria," Appl. Environ. Microbiol. 70(January 2004):52-60; http://aem.asm.org/cgi/content/abstract/70/1/52. See also: Jodi Ackerman, "Findings of Novel Nanoproperties in Selenium Produced By Bacteria Open New Area of Exploration, Findings Could Lead to Faster Electronic Devices," Press Release, Rensselaer Polytechnic Institute, 10 February 2004; http://www.rpi.edu/web/News/press_releases/2004/nanosphere.htm.

2105. O.W. Nadeau, D.W. Gump, G.M. Hendricks, D.H. Meyer, "Deposition of bismuth by *Yersinia enterocolitica*," Med. Microbiol. Immunol. (Berl.) 181(1992):145-152.

2106. M. Kowshik, N. Deshmukh, W. Vogel, J. Urban, S.K. Kulkarni, K.M. Paknikar, "Microbial synthesis of semiconductor CdS nanoparticles, their characterization, and their use in the fabrication of an ideal diode," Biotechnol. Bioeng. 78(5 June 2002):583-588.

2107. R.R. Naik, S.J. Stringer, G. Agarwal, S.E. Jones, M.O. Stone, "Biomimetic synthesis and patterning of silver nanoparticles," Nat. Mater. 1(November 2002):169-172.

2108. M. Kierans, A.M. Staines, H. Bennett, G.M. Gadd, "Silver tolerance and accumulation in yeasts," Biol. Met. 4(1991):100-106.

2109. Absar Ahmad, Satyajyoti Senapati, M. Islam Khan, Rajiv Kumar, R. Ramani, V. Srinivas, Murali Sastry, "Intracellular synthesis of gold nanoparticles by a novel alkalotolerant actinomycete, *Rhodococcus* species," Nanotechnology 14(July 2003):824-828; http://www.iop.org/EJ/abstract/-ffissn=0957-4484/-ff30=all/0957-4484/14/7/323 (abstract).

2110. D. Schuler, R.B. Frankel, "Bacterial magnetosomes: microbiology, biomineralization and biotechnological applications," Appl. Microbiol. Biotechnol. 52(October 1999):464-473; R.E. Dunin-Borkowski, M.R. McCartney, R.B. Frankel, D.A. Bazylinski, M. Posfai, P.R. Buseck, "Magnetic microstructure of magnetotactic bacteria by electron holography," Science 282(4 December 1998):1868-1870.

2111. T. Kondo, M. Nojiri, Y. Hishikawa, E. Togawa, D. Romanovicz, R.M. Brown Jr., "Biodirected epitaxial nanodeposition of polymers on oriented macromolecular templates," Proc. Natl. Acad. Sci. (USA) 99(29 October 2002):14008-14013; http://www.pnas.org/cgi/content/full/99/22/14008. See also: Helen Pearson, "Bugs trained to build circuit," Nature ScienceUpdate, 8 October 2002; http://www.nature.com/nsu/021007/021007-1.html.

2112. R.M. Brown Jr., J.H. Willison, C.L. Richardson, "Cellulose biosynthesis in Acetobacter xylinum: visualization of the site of synthesis and direct measurement of the in vivo process," Proc. Natl. Acad. Sci. (USA) 73(December 1976):4565-4569; C.H. Haigler, R.M. Brown Jr., M. Benziman, "Calcofluor white ST alters the in vivo assembly of cellulose microfibrils," Science 210(21 November 1980):903-906; C.H. Haigler, A.R. White, R.M. Brown Jr., K.M. Cooper, "Alteration of in vivo cellulose ribbon assembly by carboxymethylcellulose and other cellulose derivatives," J. Cell Biol. 94(July 1982):64-69.

2113. J. Xu, R.A. Clark, "Extracellular matrix alters PDGF regulation of fibroblast integrins," J. Cell Biol. 132(January 1996):239-249.

2114. E.E. Qwarnstrom, R.C. Page, "Development of a three-dimensional extracellular matrix synthesized by human diploid fibroblasts in vitro," J. Cell Sci. 84(August 1986):183-200.

2115. R.A. Clark, G.A. McCoy, J.M. Folkvord, J.M. McPherson, "TGF-beta 1 stimulates cultured human fibroblasts to proliferate and produce tissue-like fibroplasia: a fibronectin matrix-dependent event," J. Cell Physiol. 170(January 1997):69-80.

2116. J.C. Dallon, J.A. Sherratt, "A mathematical model for fibroblast and collagen orientation," Bull. Math. Biol. 60(January 1998):101-129.

2117. H. Yamada, T. Inazumi, S. Tajima, H. Muramatsu, T. Muramatsu, "Stimulation of collagen expression and glycosaminoglycan synthesis by midkine in human skin fibroblasts," Arch. Dermatol. Res. 289(June 1997):429-433.

2118. G. Aktas, R. Kayton, "Ultrastructural immunolocalization of basic fibroblast growth factor in fibroblasts and extracellular matrix," Histochem. Cell. Biol. 113(March 2000):227-233.

2119. V.C. Mudera, R. Pleass, M. Eastwood, R. Tarnuzzer, G. Schultz, P. Khaw, D.A. McGrouther, R.A. Brown, "Molecular responses of human dermal fibroblasts to dual cues: contact guidance and mechanical load," Cell Motil. Cytoskeleton 45(January 2000):1-9.

2120. D.S. Steinbrech, M.T. Longaker, B.J. Mehrara, P.B. Saadeh, G.S. Chin, R.P. Gerrets, D.C. Chau, N.M. Rowe, G.K. Gittes, "Fibroblast response to hypoxia: the relationship between angiogenesis and matrix regulation," J. Surg. Res. 84(15 June 1999):127-133.

2121. D. Kessler, S. Dethlefsen, I. Haase, M. Plomann, F. Hirche, T. Krieg, B. Eckes, "Fibroblasts in mechanically stressed collagen lattices assume a 'synthetic' phenotype," J. Biol. Chem. 276(28 September 2001):36575-36585.

2122. T.S. Kim, S.W. Chung, S.Y. Hwang, "Augmentation of antitumor immunity by genetically engineered fibroblast cells to express both B7.1 and interleukin-7," Vaccine 18(15 June 2000):2886-2894; T.S. Kim, S.W. Chung, S.H. Kim, B.Y. Kang, S.Y. Hwang, J.W. Lee, "Genetically engineered fibroblasts with antigen-presenting capability: efficient induction of an antigen-specific cytotoxic T-lymphocyte response and protection against tumor development in vivo," Cancer Gene Ther. 7(June 2000):861-869; T.S. Kim, S.W. Chung, S.H. Kim, S.N. Kang, B.Y. Kang, "Therapeutic anti-tumor response induced with epitope-pulsed fibroblasts genetically engineered for B7.1 expression and IFN-gamma secretion," Int. J. Cancer 87(1 August 2000):427-433.

2123. F. Grinnell, H. Fukamizu, P. Pawelek, S. Nakagawa, "Collagen processing, crosslinking, and fibril bundle assembly in matrix produced by fibroblasts in long-term cultures supplemented with ascorbic acid," Exp. Cell Res. 181(April 1989):483-491.

2124. M. Eastwood, D.A. McGrouther, R.A. Brown, "Fibroblast responses to mechanical forces," Proc. Inst. Mech. Eng. [H] 212(1998):85-92.

2125. Mark Ptashne, A Genetic Switch: Phage (Lambda) and Higher Organisms, Blackwell Science, Inc., Boston, MA, 1996.

2126. Ron Weiss, "Programming biological cells," October 1998; http://www.swiss.ai.mit/%7Erweiss/bio-programming/asplos98-talk.pdf.

2127. Ron Weiss, "Toward in-vivo digital circuits," January 1999; http://www.swiss.ai.mit/%7Erweiss/bio-programming/dimacs99-evocomp.pdf.

2128. Ron Weiss, "Digitally programmed cells," October 1999; http://www.swiss.ai.mit/%7Erweiss/bio-programming/NSFBMCmeeting99.pdf.

2129. Michael B. Elowitz, S. Leibler, "A synthetic oscillatory network of transcriptional regulators," Nature 403(20 January 2000):335-338; http://www.aph.caltech.edu/people/Repressilator.pdf.

2130. T.S. Gardner, C.R. Cantor, J.J. Collins, "Construction of a genetic toggle switch in Escherichia coli," Nature 403(20 January 2000):339-342.

2131. Ron Weiss, Thomas F. Knight, Jr., "Engineered communications for microbial robotics," June 2000; http://www.swiss.ai.mit/%7Erweiss/bio-programming/rweiss-dna6.pdf.

2132. J. Hasty, D. McMillen, J.J. Collins, "Engineered gene circuits," Nature 420(14 November 2002):224-230; http://dx.doi.org/10.1038/nature01257 (abstract).

2133. C.C. Guet, M.B. Elowitz, W. Hsing, S. Leibler, "Combinatorial synthesis of genetic networks," Science 296(24 May 2002):1466-1470, 1407-1408 (comment); http://www.aph.caltech.edu/people/CombinatorialNetworks.pdf.

2134. M.B. Elowitz, A.J. Levine, E.D. Siggia, P.S. Swain, "Stochastic gene expression in a single cell," Science 297(2002):1183-1186; http://www.aph.caltech.edu/people/Noise.pdf.

2135. J.M. Hasty, "Design then mutate," Proc. Natl. Acad. Sci. (USA) 99(24 December 2002):16516-16518.

2136. "Engineered gene circuits: A playground for physicists and mathematicians," Joint Mathematics Meetings, American Mathematical Society, 15 January 2003, Baltimore, MD; http://www.ams.org/amsmtgs/2074_abstracts/983-92-1363.pdf (abstract).

2137. Erica Klarreich, "Digital Cells: Computer circuits made of genes may soon program bacteria," Science News 163(26 April 2003); http://www.sciencenews.org/20030426/bob11.asp.

2138. Y. Yokobayashi, et al, "Evolutionary design of genetic circuits and cell-cell communication," Advances in Complex Systems (2003), in press; http://www.ee.princeton.edu/~rweiss/bio-programming/Circuits-Cell-CellComm.pdf.

2139. S. Basu, D. Karig, R. Weiss, "Engineering signal processing in cells: towards molecular concentration band detection," Eighth International Meeting on DNA Based Computers, 10-13 June 2002, Hokkaido University, Japan; http://www.ee.princeton.edu/~rweiss/bio-programming/basu-dna8.pdf.

2140. Y. Yokobayashi, R. Weiss, F.H. Arnold, "Directed evolution of a genetic circuit," Proc. Natl. Acad. Sci. (USA) 99(24 December 2002):16587-16591; http://www.pnas.org/cgi/content/abstract/99/26/16587.

2141. R. Weiss et al, "Genetic circuit building blocks for cellular computation, communications, and signal processing," Natural Computing (2003), in press; http://www.ee.princeton.edu/~rweiss/bio-programming/weiss-natural-computing-2003.pdf.

2142. Steven Schultz, "Making bacteria behave: Electrical engineer programs cells to do his bidding," Princeton Weekly Bulletin 92(7 October 2002); http://www.princeton.edu/pr/pwb/02/1007/6a.shtml.

2143. Ron Weiss homepage; http://www.ee.princeton.edu/~rweiss/ and http://www.swiss.ai.mit.edu/~rweiss/.

2144. Drew Endy, Tom Knight, Randy Rettberg, Gerald J. Sussman, "MIT 2003 IAP. Synthetic Biology Lab: Engineered Genetic Blinkers," http://syntheticbiology.org/iap/.

2145. MIT Registry of Standard Biological Parts (formerly BioBricks Alpha Data Book); http://parts.mit.edu/ or http://parts.syntheticbiology.org/.

2146. Pak Chung Wong, Kwong-kwok Wong, Harlan Foote, "Organic data memory using the DNA approach," Commun. ACM 46(January 2003):95-98; http://portal.acm.org/citation.cfm?doid=602421.602426#abstract (abstract). See also: Natasha McDowell, "Data stored in multiplying bacteria," NewScientist.com, 8 January 2003; http://www.newscientist.com/news/news.jsp?id=ns99993243.

2147. Kimberly Hamad-Schifferli, John J. Schwartz, Aaron T. Santos, Shuguang Zhang, Joseph M. Jacobson, "Remote electronic control of DNA hybridization through inductive coupling to an attached metal nanocrystal antenna," Nature 415(10 January 2002):152-156; http://www.media.mit.edu/molecular/HamadNature.pdf.

2148. Philip Ball, "Remote-control for bacteria. Radio waves switch proteins on and off," Nature ScienceUpdate, 6 December 2002; http://www.nature.com/nsu/021202/021202-12.html.

2149. W.M. Pankau, S. Mönninghoff, G. von Kiedrowski, "Thermostable and monoconjugable gold cluster by gripping with a dodekadentate thioether ligand," submitted, patent pending, 2003. See also: W. Matthias Pankau, Karen Verbist, Günter von Kiedrowski, "Phase-transfer synthesis of novel water-soluble gold clusters with tripodal thioether based ligands," Chem. Commun. (2001):519-520.

2150. J.-W. Kim, A. Malshe, S. Tung, "Bio-inspired MEMS: A novel microfluidics system actuated by biological cell motors," 2003 Institute of Biological Engineering (IBE) Annual Meeting, Athens, GA; S. Tung, J.-W. Kim, A. Malshe, C.C. Lee, R. Pooran, "A cellular motor driven microfluidic system," Tranducers'03 — 12th Intl. Conf. on Solid-State Sensors, Actuators and Microsystems, Boston, MA (acc. for publ.); J.-W. Kim, C.C. Lee, R. Pooran, S. Tung, A. Malshe, "Bio-Micro-Electro-Mechanical System (Bio-MEMS) controlled by microbial cell motors," 2003 American Society of Agricultural Engineers (ASAE) Annual International Meeting, Las Vegas, NV (acc. for present.); M. Al-Fandi, A. Malshe, J.-W. Kim, S. Tung, J. Jenkins, S. Sundaram, "Design and analysis of viscous micropump actuated using biological cell motors," ASME Intl. Mechanical Eng. Congress and R&D Expo (IMECE), Washington, D.C., 2003 (abst. subm.).

2151. "Mutant Bacteria Become Microscopic Motors," University of Arkansas, Fayetteville, 4 February 2003; http://www.sciencedaily.com/releases/2003/02/030204080010.htm.

2152. Steve Tung, personal communication to Robert A. Freitas Jr., 28 September 2003.

2153. Steven S. Smith, personal communication to Robert A. Freitas Jr., 1 October 2003.

2154. Helen Pearson, "Construction bugs find tiny work," Nature ScienceUpdate, 11 July 2003; http://www.nature.com/nsu/030707/030707-9.html.

2155. Carlo D. Montemagno, Feynman Prize award lecture, 11th Foresight Conference on Molecular Nanotechnology, Palo Alto, CA, 9-12 October 2003.

2156. Eldrid Sequeira, Alicja J. Copik, "Design and Development of A Nanoscale Microorganism Based Power Unit," paper presented at 8th Foresight Conf. on Molecular Nanotechnology, 3-5 November 2000; http://www.foresight.org/Conferences/MNT8/Abstracts/Sequeira/.

2157. "Bug-driven robots to administer drugs," BBC News, 22 November 2000; http://news.bbc.co.uk/1/hi/health/1035344.stm.

2158. Angela M. Belcher homepage, http://www.cm.utexas.edu/faculty/Belcher.html; Belcher research group website: http://www.cm.utexas.edu/belcher/.

2159. "It all falls into place…" Nature 413(2001):668.

2160. Seung-Wuk Lee, Chuanbin Mao, Christien E. Flynn, Angela M. Belcher, "Ordering of quantum dots using genetically engineered viruses," Science 296(3 May 2002):892-895; http://www.sciencemag.org/cgi/content/full/296/5569/892?ijkey=187CbPcuOaF9Q&. Comment at: C.K. Ober, "Self-assembly. Persistence pays off," Science 296(3 May 2002):859-861.

2161. Chuanbin Mao, Daniel J. Solis, Brian D. Reiss, Stephen T. Kottmann, Rozamond Y. Sweeney, Andrew Hayhurst, George Georgiou, Brent Iverson, Angela M. Belcher, "Virus-based toolkit for the directed synthesis of magnetic and semiconducting nanowires," Science 303(9 January 2004):213-217; http://www.sciencemag.org/cgi/content/full/303/5655/213.

2162. Anne Eisenberg, "Benign Viruses Shine on the Silicon Assembly Line," The New York Times, 12 February 2004; http://www.nytimes.com/2004/02/12/technology/circuits/12next.html.

2163. Sandra R. Whaley, Doug S. English, Evelyn L. Hu, Paul F. Barbara, Angela M. Belcher, "Selection of peptides with semiconductor binding specificity for directed nanocrystal assembly," Nature 405(8 June 2000):665-668. Comment at: C.A. Mirkin, T.A. Taton, "Semiconductors meet biology," Nature 405(8 June 2000):626-627; http://www.cm.utexas.edu/belcher/sandra.pdf; Angela M. Belcher homepage, http://www.cm.utexas.edu/faculty/Belcher.html; Belcher research group website: http://www.cm.utexas.edu/belcher/.

2164. S.J. Park, A.A. Lazarides, C.A. Mirkin, R.L. Letsinger, "Directed assembly of periodic materials from protein and oligonucleotide-modified nanoparticle building blocks," Angew. Chem. Int. Ed. Engl. 40(3 August 2001):2909-2912.

2165. T.D. Clark, J. Tien, D.C. Duffy, K.E. Paul, G.M. Whitesides, "Self-assembly of 10-microm-sized objects into ordered three-dimensional arrays," J. Am. Chem. Soc. 123(8 August 2001):7677-7682.

2166. Y. Yin, Y. Lu, B. Gates, Y. Xia, "Template-assisted self-assembly: a practical route to complex aggregates of monodispersed colloids with well-defined sizes, shapes, and structures," J. Am. Chem. Soc. 123(12 September 2001):8718-8729.

2167. T.D. Clark, R. Ferrigno, J. Tien, K.E. Paul, G.M. Whitesides, "Template-directed self-assembly of 10-microm-sized hexagonal plates," J. Am. Chem. Soc. 124(15 May 2002):5419-5426.

2168. Chuanbin Mao, Christine E. Flynn, Andrew Hayhurst, Rozamond Sweeney, Jifa Qi, George Georgiou, Brent Iverson, Angela M. Belcher, "Viral assembly of oriented quantum dot nanowires," Proc. Natl. Acad. Sci. (USA) 100(10 June 2003):6946-6951.

2169. G.A. Weiss, S.S. Sidhu, "Design and evolution of artificial M13 coat proteins," J. Mol. Biol. 300(30 June 2000):213-219; S.S. Sidhu, "Engineering M13 for phage display," Biomol. Eng. 18(September 2001):57-63.

2170. T. Douglas, M. Young, "Virus particles as templates for materials synthesis," Advanced Materials 11(1999):679-687; E. Gillitzer, D. Willits, M. Young, T. Douglas, "Chemical modification of a viral cage for multivalent presentation," Chem. Commun. (Camb.) 20(21 October 2002):2390-2391; T. Douglas, E. Strable, D. Willits, A. Aitouchen, M. Libera, M. Young, "Protein engineering of a viral cage for constrained nanomaterials synthesis," Advanced Materials 14(2002):415-422. See also: Anne M. Rosenthal, "Viral nanoassemblers for electronics," Scientific American online, 2 September 2002; http://www.sciam.com/article.cfm?articleID=000BEC4E-39F3-1D6E-90FB809EC5880000.

2171. E. Dujardin, C. Peet, G. Stubbs, J.N. Culver, S.E. Mann, "Organization of metallic nanoparticles using tobacco mosaic virus templates," Nano Lett. 3(2003):413-417.

2172. Qian Wang, Tianwei Lin, Liang Tang, John E. Johnson, M.G. Finn, "Icosahedral virus particles as addressable nanoscale building blocks," Angew. Chem. Int. Ed. 41(1 February 2002):459-462. See also: "Researchers at TSRI turn viruses into enhanced nanochemical building blocks," EurekAlert, 28 January 2002; http://www.eurekalert.org/pub_releases/2002-01/sri-rat012502.php.

2173. M.T. Klem, D. Willits, M. Young, T. Douglas, "2-D array formation of genetically engineered viral cages on Au surfaces and imaging by atomic force microscopy," J. Am. Chem. Soc. 125(10 September 2003):10806-10807.

2174. T. Douglas, M. Young, "Host-guest encapsulation of materials by assembled virus protein cages," Nature 393(14 May 1998):152-155; G. Basu, M. Allen, D. Willits, M. Young, T. Douglas, "Metal binding to cowpea chlorotic mottle virus using terbium(III) fluorescence," J. Biol. Inorg. Chem. 8(September 2003):721-725; M. Allen, D. Willits, M. Young, T. Douglas, "Constrained synthesis of cobalt oxide nanomaterials in the 12-subunit protein cage from *Listeria innocua*," Inorg. Chem. 42(6 October 2003):6300-6305.

2175. Ryan W. Drum, Richard Gordon, "Star Trek replicators and diatom nanotechnology," Trends in Biotechnol. 21(August 2003):325-328; http://tibtec.trends.com/.

2176. R. Gordon, B.D. Aguda, "Diatom morphogenesis: natural fractal fabrication of a complex microstructure," in G. Harris, C. Walker, eds., Proc. Annual Intl. Conf. IEEE Engineering in Medicine and Biology, Part 1/4: Cardiology and Imaging, 4-7 November 1988, New Orleans, LA, IEEE, New York, pp. 273-274.

2177. R. Gordon, R.W. Drum, "The chemical basis for diatom morphogenesis," Int. Rev. Cytol. 150(1994):243-372, 421-422 (addendum).

2178. L.A. Sowards et al., "Ordered silica nanostructure created by reaction of tetrahydroxysilane solution with peptide isolated from the diatom C. fusiformis," Abstr. Am. Chem. Soc. 221(2001):232-BIOT.

2179. K.H. Sandhage et al, "Novel, bioclastic route to self-assembled, 3-D, chemically tailored meso/nanostructures: Shape-preserving reactive conversion of biosilica (diatom) microshells," Adv. Mat. 14(2002):429-433.

2180. Liz Kalaugher, "Diatomists shell out on nanotechnology," Nanotechweb.org, 2003; http://nanotechweb.org/articles/feature/2/2/2/1. See also New Scientist 181(17 January 2004):26.

2181. J.N. Cha, G.D. Stucky, D.E. Morse, T.J. Deming, "Biomimetic synthesis of ordered silica structures mediated by block copolypeptides," Nature 403(20 January 2000):289-292.

2182. R.P. Feynman, "There's Plenty of Room at the Bottom," Eng. and Sci. (CalTech) 23(February 1960):22-36. Reprinted in B.C. Crandall, James Lewis, eds., Nanotechnology: Research and Perspectives, MIT Press, Cambridge, MA, 1992, pp. 347-363, and in D.H. Gilbert, ed., Miniaturization, Reinhold, New York, 1961, pp. 282-296. See also: http://www.zyvex.com/nanotech/feynman.html.

2183. Richard P. Feynman, "The wonders that await a micro-microscope," Saturday Review 43(1960):45-47.

2184. Theodor Seuss Geisel (Dr. Seuss), The Cat in the Hat Comes Back, Beginner Books, Inc., New York, 1958.

2185. Ed Regis, Nano: The Emerging Science of Nanotechnology, Little, Brown & Company, New York, 1995.

2186. Mehran Mehregany, Yu-Chong Tai, "Surface micromachined mechanisms and micromotors," J. Micromech. Microeng. 1(1991):73-85.

2187. V.R. Dhuler, M. Mehregany, S.M. Philips, J.H. Lang, "A comparative study of bearing design and operational environments for harmonic side-drive micromotors," Proc. IEEE Micro Electro Mechanical Systems, Travemunde, Germany, 1992, pp. 171-176.

2188. Doug Stewart, "New Machines are Smaller than a Hair, and Do Real Work," Smithsonian 21(November 1990):85-96.

2189. Christian Burrer, Jaume Esteve, Emilio Lora-Tamayo, "Resonant silicon accelerometers in bulk micromachining technology — an approach," J. Microelectromech. Syst. 5(June 1996):122-129.

2190. Ezekiel J.J. Kruglick, Brett A. Warneke, Kristofer S.J. Pister, "CMOS 3-axis accelerometers with integrated amplifier," Proc. IEEE Micro Electro Mechanical Systems Workshop 1998 (MEMS '98).

2191. M. Kraft, C.P. Lewis, T.G. Hesketh, "Closed loop silicon accelerometers," IEE Proc. Circuits Devices Syst. 145(1998):325-331.

2192. L.S. Fan, Y.C. Tai, R.S. Miller, "Integrated movable micromechanical structures for sensors and actuators," IEEE Trans. Electron. Devices ED-35(1988):724-730.

2193. Roberto Dizon, Hongtao Han, Armistead G. Russell, Michael L. Reed, "An ion milling pattern transfer technique for fabrication of three-dimensional micromechanical structures," J. Microelectromech. Syst. 2(December 1993):151-159.

2194. K.F. Hale, C. Clarke, R.F. Duggan, B.E. Jones, "Incremental control of a valve actuator employing optopneumatic conversion," Sensors and Actuators A21-A23(1990):207-210.

2195. Shuichi Shoji, Masayoshi Esashi, "Microfabrication and Microsensors," Appl. Biochem. Biotech. 41(1993):21-34.

2196. M. Mehregany, K.J. Gabriel, W.S. Trimmer, "Integrated fabrication of polysilicon mechanisms," IEEE Trans. Electron. Devices ED-35(1988):719-723.

2197. Paul L. Bergstrom, Jin Ji, Yu-Ning Liu, Massoud Kaviany, Kensall D. Wise, "Thermally driven phase-change microactuation," J. Microelectromechanical Systems 4(January-March 1995):10-17.

2198. M. Fleischer, H. Meixner, "Ultrasonic motors," Mechatronics 1(1991):403-415.

2199. V.P. Jaecklin, C. Linder, N.F. de Rooij, J.-M. Moret, R. Vuilleumier, "Optical microshutters and torsional micromirrors for light modulator arrays," Proceedings 6th IEEE Micro Electro Mechanical Systems, IEEE Robotics and Automation Society, 1993, pp. 124-127.

2200. Jon Cohen, "Interdisciplinary Talkfest Prompts Flurry of Questions," Science 270(24 November 1995):1294.

2201. Kaigham J. Gabriel, "Engineering Microscopic Machines," Sci. Amer. 273(September 1995):150-153.

2202. S.S. Lee, L.Y. Lin, K.S.J. Pister, M.C. Wu, H.C. Lee, P. Grodzinski, "Passively aligned hybrid integration of 8 x 1 micromachined micro-Fresnel lens arrays and 8 x 1 vertical-cavity surface-emitting laser arrays for free-space optical interconnect," IEEE Photonics Technol. Lett. 7(September 1995):1031-1033.

2203. P. Greiff, B. Boxenhorn, T. King, L. Niles, "Silicon monolithic micromechanical gyroscope," 1991 Intl. Conf. on Solid-State Sensors and Actuators (Transducers '91), San Francisco, CA, June 1991, pp. 966-968.

2204. I.A. Waitz, G. Gauba, Y.-S. Tzeng, paper presented at the A.S.M.E. International Engineering Congress and Exposition, Atlanta, November 1996.

2205. A.H. Epstein, S.D. Senturia, "Macro power from micro machinery," Science 276(23 May 1997):1211.

2206. Yogesh Gianchandani, Khalil Najafi, "Batch-assembled multi-level micromachined mechanisms from bulk silicon," J. Micromech. Microeng. 2(1992):80-85.

2207. Chang-Jin Kim, Albert P. Pisano, Richard S. Muller, Martin G. Lim, "Polysilicon microgripper," Sensors and Actuators A 33(1992):221-227. See also: "Silicon-processed overhanding microgripper," J. Microelectromech. Syst. 1(March 1992):31-36 and "Design, fabrication and testing of a polysilicon microgripper," Microstructures, Sensors, and Actuators, ASME, New York, DSC-19(1990):99-109.

2208. "Smoovy Motor Applications: A 1 cc mobile robot," LAMI Miniature Robots and Subsystems Group, June 1997, http://diwww.epfl.ch/w3lami/mirobots/smoovy.html.

2209. "Microrobots: Features of Jemmy, our tiny 1 cm^3 robot," LAMI Miniature Robots and Subsystems Group, 31 August 1998, http://lamiwww.epfl.ch/lami/mirobots/1cubes.html.

2210. G. Caprari, T. Estier, R. Siegwart, "Fascination of down scaling — Alice the sugar cube robot," J. Micromechatronics 1(July 2002):177-189; also published in Workshop Proceedings on Mobile Micro-Robots, IEEE Intl. Conf. on Robotics and Automation, San Francisco, CA, April 2000, pp. 24-28; http://asl.epfl.ch/aslInternalWeb/ASL/publications/uploadedFiles/caprariICRA00.pdf.

2211. G. Caprari, T. Estier, R. Siegwart, "Design and control of the mobile micro robot Alice," Proc. 2nd Intl. Symp. on Autonomous Minirobots for Research and Edutainment, Brisbane, Australia (AMiRE'2003), pp. 23-32; http://asl.epfl.ch/aslInternalWeb/ASL/publications/uploadedFiles/DesignControl.pdf.

2212. Akihiko Teshigahara, Masakane Watanabe, Nobuaki Kawahara, Yoshinori Ohtsuka, Tadashi Hattori, "Performance of a 7-mm microfabricated car," J. Microelectromech. Syst. 4(June 1995):76-80.

2213. Harumi Suzuki, Nobuyuki Ohya, Nobuaki Kawahara, Masao Yokoi, Sigeru Ohyanagi, Takashi Kurahashi, Tadashi Hattori, "Shell-body fabrication for micromachines," J. Micromech. Microeng. 5(1995):36-40.

2214. N. Lobontiu, M. Goldfarb, E. Garcia, "A piezoelectric-driven inchworm locomotion device," Mechanism and Machinery Theory 36(2001):425-443.

2215. Shin-ichiro Kawakita, "Development of autonomous mobile microrobot," Denso Corp., 1999; http://akseli.tekes.fi/Resource.phx/tivi/presto/tapahtunutta.htx.Doc.doc.3.pdf.

2216. Takanari Sasaya, T. Shibata, Nobuaki Kawahara, "In-pipe wireless micro robot," Transducers 99 Digest of Technical Papers, Vol. 2, 1999, pp. 1058-1061; Kazuhiro Tsuruta, Takanari Sasaya, Nobuaki Kawahara, "In-pipe wireless micro robot," J. Micromechatronics 1(July 2002):263-272.

2217. Michael Gogola, Gregory Fisher, Michael Goldfarb, Ephrahim Garcia, "The development of two piezoelectrically actuated mesoscale robot quadrupeds," SPIE Symposium on Microrobotics and Microassembly, Vol. 3834, September 1999, pp. 76-84; Michael Goldfarb, Michael Gogola, Gregory Fischer, Ephrahim Garcia, "Development of a piezoelectrically-actuated mesoscale robot quadruped," J. Micromechatronics 1(July 2002):205-219.

2218. Raymond H. Byrne, Douglas R. Adkins, Steven E. Eskridge, John J. Harrington, Edwin J. Heller, Johnny E. Hurtado, "Miniature mobile robots for plume tracking and source localization research," J. Micromechatronics 1(July 2002):253-261.

2219. K. Suzumori, T. Miyagawa, M. Kimura, Y. Hasegawa, "Micro inspection robot for 1-in pipes," IEEE/ASME Trans. Mechatron. 4(1999):286-292.

2220. "Japanese Introduce Ant-Size Robot," Associated Press report, 21 June 1999; http://www.salonmagazine.com/tech/log/1999/06/21/robot/index.html.

2221. "Millimeter-size Robot: a Prototype for Microscopic Machines," BetterHumans, 17 February 2003; http://www.betterhumans.com/News/news.aspx?articleID=2003-02-17-1.

2222. Kristofer S.J. Pister, "Research Projects," May 2003 download; http://www-bsac.eecs.berkeley.edu/~pister/projects.html. See also: I.N. Tahhan, Y. Zhuang, K.F. Bohringer, K.S.J. Pister, K. Goldberg, "MEMS fixtures for handling and assembly of microparts," Proc. Micromachined Devices and Components V, Santa Clara, CA, 20-21 September 1999, Vol. 3876, pp. 129-139.

2223. T. Ebefors, J. Mattson, E. Kalvesten, G. Stemme, "A Walking Silicon Micro-Robot," 10th Intl. Conf. on Solid-State Sensors and Actuators (TRANSDUCERS '99), pp. 1202-1205, Sendai Japan, Jun. 7-10, 1999. See also: http://www.s3.kth.se/mst/research/gallery/microrobot_video.html.

2224. Ranjana Sahai, Jusuk Lee, Ron Fearing, "Towards automatic assembly of sub-centimeter millirobot structures," Third Intl. Workshop on Microfactories, Minneapolis, MN, 16-18 September 2002; http://robotics.eecs.berkeley.edu/~ronf/PAPERS/autoassemblyv8.pdf.

2225. Ron Fearing, "Desktop Rapid Prototyping Millirobots," http://robotics.eecs.berkeley.edu/~ronf/desktop.html.

2226. J.A. Thompson, R.S. Fearing, "Automating microassembly with ortho-tweezers and force sensing," in IEEE/RSJ Intl. Conf. on Intelligent Robots and Systems (IROS), Maui, HI, 2001.

2227. Ron Fearing, personal communication to Robert A. Freitas Jr., 5 August 2003.

2228. "An Architecture for Agile Assembly," Microdynamic Systems Laboratory, Carnegie Mellon University, August 8, 2002; http://www-2.cs.cmu.edu/afs/cs/project/msl/www/minifactory/minfact_desc.html.

2229. R. L. Hollis, J. Gowdy, "Miniature Factories for Precision Assembly," Intl. Workshop on Microfactories, Tsukuba, Japan, 7-9 December 1998, pp. 9-14; http://www-2.cs.cmu.edu/afs/cs/project/msl/www/publications/tsu98.pdf.

2230. H. Aoyama, F. Iwata, A. Sasaki, "Desktop flexible manufacturing system by movable miniature robots," Proc. Intl. Conf. Robotics and Automation, 1995, pp. 660-665.

2231. Y. Hatamura, M. Nakao, T. Sato, "Construction of nano manufacturing world as a desk-top factory," Microsystem Technologies 1(1995):155-162.

2232. "Microfactory Technologies," Advanced Machine Technology, Mechanical Engineering Laboratory, Agency of Industrial Science and Technology (AIST); http://www.mel.go.jp/e/3.html.

2233. Antoine Ferreira, "Design of a flexible conveyer microrobot with electromagnetic field-based friction drive control for microfactory stations," J. Micromechatronics 1(September 2000):49-66.

2234. Susan Finger, "Rapid Design Through Virtual and Physical Prototyping," Robotics Institute, Carnegie Mellon University; http://www-2.cs.cmu.edu/~radproto/ and http://www.ri.cmu.edu/projects/project_185.html.

2235. Ramon Estana, "Miniaturised Co-operative Robots advancing towards the Nano range," MiCRoN Project, funded by the Future and Emerging Technologies arm of the IST Programme of the European Commission, 7 February 2002; http://wwwipr.ira.uka.de/~micron/index.html.

2236. Innovation On Demand, Inc. Web Site; http://www.innovation-on-demand.com.

2237. A.D. Johnson, M. Fanucchi, V. Gupta, V. Martynov, V.Galhotra, K. Clements, "TiNi as a nano-actuator: experimental verification of excitation by electron-beam heating," 2003; http://www.innovation-on-demand.com/Papers/Nanoactuation_Paper.htm.

2238. Institute for Machine Tools and Industrial Management — iwb Munich Microassembly Research; http://www.iwb.tum.de/iwb_lang_en_name_Forschung_page_18.html.

2239. Micro Assembly Automation Laboratory, Lawrence Livermore National Laboratory, 16 December 1996; http://www.llnl.gov/eng/ee/erd/maal/maalhome.html.

2240. Department of Micro System Engineering, Nagoya University; http://www.mech.nagoya-u.ac.jp/MICRO/index-e.html.

2241. S.J. Ralis, B.Vikramaditya, B.J. Nelson, "Micropositioning of a weakly calibrated microassembly system using coarse-to-fine visual servoing strategies," IEEE Trans. on Electr. Packaging Manufacturing 23(2000):123-131.

2242. G. Yang, J.A. Gaines, B.J. Nelson, "A flexible experimental workcell for efficient and reliable wafer-level 3-D micro-assembly," in IEEE Intl. Conf. on Robotics and Automation (ICRA), Seoul, South Korea, 2001.

2243. Precision Micro Assembly Laboratory, The Intelligent Systems & Robotics Center, Sandia National Laboratories, 8 July 2001; http://www.sandia.gov/isrc/precmicroassy.html.

2244. "Microrobotics and Millirobotics Research," Robotics and Intelligent Machines Laboratory, University of California at Berkeley, 26 February 2002; http://robotics.eecs.berkeley.edu/~ronf/milli-robot.html.

2245. Advanced Microsystems Laboratory, University of Minnesota; http://www.me.umn.edu/divisions/design/adv_microsystems/index2.htm.

2246. "Microrobotics and Robotization of Manufacturing Processes," Center of High Technologies in Manufacturing Systems, Ufa State Aviation Technical University (USATU); http://www.ugatu.ac.ru/ugatu.new/DR/eng/english/subject/rarnan/index.htm.

2247. "NIST-ATP Project for Assembly of Microsystems," Zyvex Corp., 2003; http://www.zyvex.com/Research/projects.html#NISTProject.

2248. Zyvex Corp., "Research and Development Activities," 8 September 2003; http://www.zyvex.com/Research/projects.html.

2249. A. Mardanov, J. Seyfried, S. Fatikow, "An automated assembly system for a microassembly station," Beitrag in Zeitschrift 38(1999):93-102; S. Fatikow, U. Rembold, "An automated microrobot-based desktop station for micro assembly and handling of micro-objects," Proc. IEEE Conf. on Emerging Technologies and Factory Automation (EFTA '96), Kauai, HI, 18-21 November 1996, pp. 586-592.

2250. N. Kawahara, T. Suto, T. Hirano, Y. Ishikawa, T. Kitahara, N. Oyama, T. Ataka, "Microfactories: new applications of micromachine technology to the manufacture of small products," Res. J. Microsystem-Technol. 3(1997):37-41; T. Kitahara, K. Ashida, M. Tanaka, Y. Ishikawa, N. Oyama, Y. Nakazawa, "Microfactory and microlathe," Proc. Intl. Workshop on Microfactories, 1999, pp. 1-8..

2251. International Workshops on Microfactories; http://www.ri.cmu.edu/events/iwmf02/ (2002), http://www-samlab.unine.ch/iwmf2000/ (2000), http://www.aist.go.jp/MEL/keiji/HPiwmf/IWMF98.htm (1998).

2252. Workshop on Micro/Meso-Mechanical Manufacturing (M^4), Northwestern University and NSF, 16-17 May 2000; http://www.mech.nwu.edu/MFG/AML/M4/Start-M4.html.

2253. Ken R. Shoulders, "On microelectronic components, interconnections, and system fabrication," Proc. Western Joint Computer Conference, National Press, Palo Alto, CA, 1960, pp. 251-258.

2254. Ken R. Shoulders, "Microelectronics using electron-beam-activated machining techniques," in Franz Alt, ed., Advances in Computers, Academic Press, New York, 1961, pp. 135-293.

2255. Ken R. Shoulders, "On microelectronic components, interconnections, and system fabrication," in C.A. Muses, ed., Aspects of the Theory of Artificial Intelligence, Plenum Press, New York, 1962, pp. 217-235.

2256. Ken R. Shoulders, "Toward complex systems," in Microelectronics and Large Systems, Spartan Books, Washington, DC, 1965, pp. 97-128.

2257. M. Ruhrig, S. Porthun, J.C. Lodder, S. McVitie, L.J. Heyderman, A.B. Johnston, J.N. Chapman, "Electron beam fabrication and characterization of high-resolution magnetic force microscopy tips," J. Appl. Phys. 79(1996):2913-2919.

2258. Marc Madou, Fundamentals of Microfabrication, CRC Press, Boca Raton, FL, 1997.

2259. W.H. Brunger, K.T. Kohlmann, "E-beam induced fabrication of microstructures," Proc. IEEE Microelectromechanical Systems (MEMS'92), Travemunde, Germany, 1992, pp. 168-170.

2260. P.C. Hoyle, J.R.A. Cleaver, H. Ahmed, "Electron beam induced deposition from W(CO)6 at 2 to 20 keV and its applications," J. Vac. Sci. Technol. B 14(1996):662.

2261. N.A. Kislov, I.I. Khodos, E.D. Ivanov, J. Barthel, "Electron-beam-induced fabrication of metal-containing nanostructures," Scanning 18(1996):114-118.

2262. Hiroshi Hiroshima, Norihito Suzuki, Naomi Ogawa, Masanori Komuro, "Conditions for fabrication of highly conductive wires by electron-beam-induced deposition," Jpn. J. Appl. Phys. 38(30 December 1999):7135-7139.

2263. F. Cicoira, P. Hoffmann, "Focused electron-beam deposition of three dimensional free standing nanometer structures," Institute of Applied Optics, DMT-IOA, EPFL, CH-1015, Lausanne, Switzerland, June 1999; http://dmtwww.epfl.ch/ioa/reports/Hoffmann/Hoffmann98-2.pdf.

2264. K.L. Lee, A.F. Secord, L. Landstein, J. Vac. Sci. Technol. B 9(1991):3562.

2265. P. Boggild, T.M. Hansen, C. Tanasa, F. Grey, "Fabrication and actuation of customized nanotweezers with a 25 nm gap," Nanotechnology 12(September 2001):331-335.

2266. T. Ooi, K. Matsumoto, M. Nakao, M. Otsubo, S. Shirakata, S. Tanaka, Y. Hatumura, Proc. MEMS 2000, pp. 580-583.

2267. "Three-Dimensional Nanofabrication Using Electron Beam Lithography — The world's smallest globe with a resolution 100 times higher than previously possible," NTT News Release, 2 February 2004; http://www.ntt.co.jp/news/news04e/0402/040202.html.

2268. Hans W.P. Koops, "Rapid prototyping and structure generation using three-dimensional nanolithography with electron beam induced chemical reactions," Paper No. 5116-52, SPIE Conference 5116, Microtechnologies for the New Millennium 2003, 19-21 May 2003, Maspalomas, Gran Canaria, Canary Islands, Spain, 2003.

2269. T. Fujii, M. Suzuki, M. Miyashita, M. Yamaguchi, T. Onuki, H. Nakamura, T. Matsubara, H. Yamada, K. Nakayama, "Micropattern measurement with an atomic force microscope," J. Vac. Sci. Technol. B 9(1991):666.

2270. Hans W.P. Koops, Johannes Kretz, Michael Rudolph, Markus Weber, Gerold Dahm, Kam L. Lee, "Characterization and application of materials grown by electron-beam-induced deposition," Jpn. J. Appl. Phys. 33(30 December 1994):7099-7107.

2271. N. Miura, H. Ishii, J.-I. Shirakashi, A. Yamada, M. Konagai, "Electron-beam-induced deposition of carbonaceous microstructures using scanning electron microscopy," Proceedings of the 8th International Conference on Solid Films and Surfaces held in Osaka, Japan, July 1996, Appl. Surf. Sci. 113/114(17 April 1997):269-273.

2272. K. Wiesauer, G. Springholza, "Fabrication of semiconductor nanostructures by nanoindentation of photoresist layers using atomic force microscopy," J. Appl. Phys. 88(15 December 2000):7289-7297; http://www.hlphys.uni-linz.ac.at/hl/perskarin/publikat/jap88_7289_00_nano.pdf.

2273. Min-Feng Yu, Oleg Lourie, Mark J. Dyer, Katerina Moloni, Thomas F. Kelly, Rodney S. Ruoff, "Strength and breaking mechanism of multiwalled carbon nanotubes under tensile load," Science 287(28 January 2000):637-640; MinFeng Yu, Mark J. Dyer, George D. Skidmore, Henry W. Rohrs, XueKun Lu, Kevin D. Ausman, James R. Von Ehr, Rodney S. Ruoff, "Three-dimensional manipulation of carbon nanotubes under a scanning electron microscope," Nanotechnology 10(September 1999):244-252.
2274. P. Boggild, T.M. Hansen, K. Molhave (Mikroelektronik Centret, Technical University of Denmark), "Nanotweezers for manipulation of free-hanging nanowires," abstract FF14, http://www.nbi.dk/dfs/abs2001final/ff14.html; presentation at Physics and Industrial Innovation Session, Chairman F. Grey (Mikroelektronik Centret, Technical University of Denmark), sponsored by Danish Physical Society, 2001; http://www.nbi.dk/dfs/abs2001final/ff00.html.
2275. B.F.G. Johnson, K.M. Sanderson, D.S. Shephard, D. Ozkaya, W. Zhou, H. Ahmed, M.D. R. Thomas, L. Gladden, M. Mantle, "Electron beam induced formation of nanoparticle chains and wires from a ruthenium cluster polymer," Chem. Commun. (2000):1317-1318.
2276. Hans W. Koops, M. Weber, C. Schoessler, A. Kaja, "Three-dimensional additive electron beam lithography," in Benedykt W. Licznerski, Andrzej Dziedzic, eds., Metal/Nonmetal Microsystems: Physics, Technology, and Applications, SPIE Proceedings Vol. 2780, SPIE — The International Society for Optical Engineering, Bellingham, WA, 1996, Paper #2780-78, pp. 388-395.
2277. Wolfgang Fritzsche, Konrad J. Bohm, Eberhard Unger, J. Michael Kohler, "Making electrical contact to single molecules," Nanotechnology 9(September 1998):177-183.
2278. Wolfgang Fritzsche, J. Michael Kohler, Konrad J. Bohm, Eberhard Unger, Thomas Wagner, Remo Kirsch, Michael Mertig, Wolfgang Pompe, "Wiring of metalized microtubules by electron beam-induced structuring," Nanotechnology 10(September 1999):331-335; http://www.ipht-jena.de/BEREICH_3/abt32/b3/english/molnano/pdf/23.pdf.
2279. Ivo Utke, B. Dwir, K. Leifer, F. Cicoira, P. Doppelt, P. Hoffmann, E. Kapon, "Electron beam induced deposition of metallic tips and wires for microelectronics applications," Microelectronics Engineering (2000).
2280. H.W.P. Koops, C. Schoessler, A. Kaya, M. Weber, "Conductive dots, wires, and supertips for field electron emitters produced by electron-beam induced deposition on samples having increased temperature," J. Vac. Sci. Tech. B 14(1996):4105-4109.
2281. C. Schoessler, H.W.P. Koops, "Nanostructured integrated electron source," J. Vac. Sci. Technol. B 16(1998):862.
2282. H.W. Fink, "Mono-atomic tips for scanning tunneling microscopy," IBM J. Res. Develop. 30(1986):460-465.
2283. A.G. Rinzler, J.H. Hafner, P. Nikolaev, L. Lou, S.G. Kim, D. Tomanek, P. Nordlander, D.T. Colbert, R.E. Smalley, "Unraveling nanotubes: field emission from an atomic wire," Science 269(15 September 1995):1550-1553.
2284. M. Weber, M. Rudolph, J. Kretz, H.W.P. Koops, "Electron-beam induced deposition for fabrication of vacuum field emitter devices," 7th IVMC, 1994, p. 395.
2285. J. Kretz, M. Rudolph. H.W. Koops, "Three dimensional structurization by additive lithography, analysis of deposits using TEM and EDX, and application for field emitter. tips," Microelectronic Engineering 23(1994):477-481.
2286. M. Takai, H. Morimoto, T. Kishimoto, S. Lipp, L. Frey, H. Ryssel, S. Yura, A. Hosono, S. Okuda, "Electron emission from gated Pt emitters fabricated by electron beam induced deposition," IVMC'96 Technical Digest, 1996, p. 657.
2287. Hiroji Morimoto, Takehisa Kishimoto, Mikio Takai, Shinsuke Yura, Akihiko Hosono, Soichiro Okuda, Stephan Lipp, Lothar Frey, Heiner Ryssel, "Electron-beam-induced deposition of Pt for field emitter arrays," Jpn. J. Appl. Phys. 35(30 December 1996):6623-6625.
2288. H.W.P. Koops, "Novel field emission devices produced by electron-beam induced deposition," IVESC'98 Session Program, The 2nd International Vacuum Electron Sources Conference, 7-10 July 1998, Tsukuba, Japan.
2289. Filip Floreani, H.W.P. Koops, W. Elsabera, "Operation of high power field emitters fabricated with electron beam induced deposition," presented Wednesday, 27 September 2000 at the EuroFE2000 Scientific Program, 25-29 September 2000, Segovia, Spain; http://www.cientifica.com/cientifica/frameworks/generic/public_users/eurofe/EuroFE2k/abstracts/floreani.pdf.
2290. J.T.L. Thong, C.H. Oon, "Electron emission from electron beam induced deposition tips," presented at the Second IEEE International Vacuum Electronics Conference, 2-4 April 2001, Noordwijk, The Netherlands.
2291. N. Silvis-Cividjian, C.W. Hagen, P. Kruit, "Resolution limits in electron beam induced deposition (EBID)," Annual Report Nederlandse Vereniging voor Microscopie, 7-8 December 2000, pp. 184-185.
2292. Hans W. Koops, "Photonic crystals built by three-dimensional additive lithography enable integrated optics of high density," in Francis T. Yu, Shizhuo Yin, eds., Photorefractive Fiber and Crystal Devices: Materials, Optical Properties, and Applications II, SPIE Proceedings Vol. 2849, SPIE — The International Society for Optical Engineering, Bellingham, WA, 1996, Paper #2849-29, pp. 248-256.
2293. M. Weber, M. Rudolph, J. Kretz, H.W.P. Koops, J. Vac. Sci. Technol. B 13(1995):461-464.
2294. IBM Zurich Research laboratory, "Assembly tool for molecular structures," 2001; http://www.zurich.ibm.com/st/nanoscience/assembly.html.
2295. B.K. Dey, M. Shapiro, P. Brumer, "Coherently controlled nanoscale molecular deposition," Phys. Rev. Lett. 85(9 October 2000):3125-3128.
2296. J. A. van Kan, A. A. Bettiol, F. Watt, "Three-dimensional nanolithography using proton beam writing," Appl. Phys. Lett. 83(2003): 1629.
2297. W. Hansel, P. Hommelhoff, T.W. Hansch, J. Reichel, "Bose–Einstein condensation on a microelectronic chip," Nature 413(4 October 2001):498-501; http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v413/n6855/full/413498a0_fs.html.
2298. Masahiro Muraoka, Thomas W. Bell, Stephen L. Gillett, "Ferrocene intercalation into hydrophobic monolayers: toward light-driven molecular assembly," presentation at the Ninth Foresight Conference on Molecular Nanotechnology, 9-11 November 2001; http://www.foresight.org/Conferences/MNT9/Abstracts/Muraoka/index.html.
2299. Fujio Shimizu, S. Mitake, J. Fujita, "Interferometric modulation of an atomic beam by an electric field: a phase hologram for atoms," Phys. Rev. Lett. 84(1 May 2000):4027-4030; brief summary in Eric J. Lerner, "Holography with Atoms," The Industrial Physicist, October 2000, pp. 10-11, at http://www.aip.org/tip/INPHFA/vol-6/iss-5/p8.pdf. See also: Hilmar Oberst, Shigenori Kasashima, Fujio Shimizu, Victor I. Balykin, "Atomic matter wave scanner," arXiv:physics/0210036v2 (9 October 2002) http://arxiv.org/pdf/physics/0210036, poster presentation at the 5th Laser Cooling Workshop, 9 January 2003.
2300. D.Z. Albert, "On quantum-mechanical automata," Phys. Lett. 98A(1983):249-252.
2301. Seth Lloyd, "A potentially realizable quantum computer," Science 261(17 September 1993):1569-1571.
2302. Vladimir Kvasnicka, Jiri Pospichal, T. Kalab, "A study of autoreplicators and hypercycles by typogenetics," in J. Kelemen, P. Sosik, eds., Advances in Artificial Life (ECAL 2001), LNAI 2159, Springer-Verlag, New York, 2001, pp. 37-54; http://link.springer.de/link/service/series/0558/bibs/2159/21590037.htm (abstract).
2303. Vladimir Kvasnicka, Jiri Pospichal, "Autoreplicators and hypercycles in typogenetics," J. Chem. Structure (Theochem) 547(2001):119-138.
2304. Ken C. Lynch, "Self-Reference in Programming and Genetics," http://www.cs.rit.edu/~kcl8605/self-ref.html.
2305. Harold C. Morris, "Typogenetics: A logic for artificial life," in Christopher G. Langton, ed., Volume VI of Santa Fe Institute Studies in the Sciences of Complexity, Addison-Wesley, New York, 1989, pp. 369-395.
2306. Andrew J. Snare, "Typogenetics," undergraduate research project, School of Computer Science and Software Engineering (CSSE), Monash University, November 1999; http://www.csse.monash.edu.au/hons/projects/1999/Andrew.Snare/ (website) and http://www.csse.monash.edu.au/hons/projects/ 1999/Andrew.Snare/thesis.pdf (paper).
2307. Louis Varetto, "Typogenetics: An artificial genetic system," J. Theor. Biol. 160(1993):185-205.
2308. Tim J. Hutton, "Evolvable self-replicating molecules in an artificial chemistry," Artificial Life 8(Fall 2002):341-356; http://mitpress.mit.edu/catalog/item/default.asp?sid=2AC0A07D-41B4-44CE-AB40-CAA5E0D78F32&ttype=6&tid=10036 (abstract). See also "Squirm3" website: http://www.eastman.ucl.ac.uk/~thutton/Evolution/Squirm3/variant5/ (includes online simulation).
2309. Toyomasa Hatakeyama, Tsuyoshi Nomoto, "Movable finite automaton models for DNA transcription," (Institute of Electronics, Information and Communication Engineers, Japan) IEICE Trans. Inf. & Syst. J80-D-II(November 1997):3069-3076; http://www.ieice.org/iss/Abstracts/data/97/11/html/97_11_D-II_PAPERS_20.html.

2310. William Illsey Atkinson, Nanocosm: Nanotechnology and the Big Changes Coming from the Inconceivably Small, AMACOM, New York, 2003.

2311. Eric Drexler, "Molecular Technology and Cell Repair Machines," lecture presented at the 1985 Lake Tahoe Life Extension Festival, 25 May 1985; reprinted and published in Claustrophobia Magazine (August-October 1985) and Cryonics (Dec 1985 - January 1986).

2312. Mark Avrum Gubrud, "Back to basics of assembler theory," online posting at nanotalk@listserv.sc.edu, 26 June 2003.

2313. K. Eric Drexler, "Introduction to Nanotechnology," in Markus Krummenacker, James Lewis, eds., Prospects in Nanotechnology: Toward Molecular Manufacturing, John Wiley & Sons, New York, 1995, pp. 1-22.

2314. Foresight Institute, "Feynman Grand Prize," http://www.foresight.org/GrandPrize.0.html.

2315. R.C. Merkle, "Molecular Manufacturing: Adding Positional Control to Chemical Synthesis," Chemical Design Automation News 8(September/October 1993):1 et seq; http://nano.xerox.com/nanotech/CDAarticle.html.

2316. Geoff I. Leach, Ralph C. Merkle, "Crystal Clear: A Molecular CAD Tool," Nanotechnology 5(1994):168-171; http://www.cs.rmit.edu.au/~gl/research/nano/crystal.html.

2317. K. Eric Drexler, Ralph C. Merkle, "Simple Pump Selective for Neon," http://www.imm.org/Parts/Parts1.html; see also at: http://science.nas.nasa.gov/Groups/Nanotechnology/gallery/pump/pumpWhite.jpg.

2318. K. Eric Drexler, Ralph C. Merkle, "A Fine-Motion Controller for Molecular Assembly," http://www.imm.org/Parts/Parts2.html; see also at: http://science.nas.nasa.gov/Groups/Nanotechnology/archive/Drexler/fineMotionController/whiteBackground.jpg.

2319. N.G. Chopra, L.X. Benedict, V.H. Crespi, M.L. Cohen, S.G. Louie, A. Zettl, "Fully collapsed carbon nanotubes," Nature 377(1995):135-138.

2320. Sergey Mishaylovich Krylov, "Prospects of formal technology and nano-technology," 2000; http://www.cyber.org.ru/ft/prosfte.htm or http://sstu.samara.ru/~vt/prosfte.htm (English language version), http://sstu.samara.ru/~vt/prospft.htm (Russian language version).

2321. Ilian Bonev, "What is Going on With Parallel Robots," Robotics Online, accessed September 2003; http://www.roboticsonline.com/public/articles/articlesdetails.cfm?id=798.

2322. Ralph C. Merkle, Robert A. Freitas Jr., "Theoretical analysis of a carbon-carbon dimer placement tool for diamond mechanosynthesis," paper presented at the 10th Foresight Conference on Molecular Nanotechnology, October 2002; http://www.foresight.org/Conferences/MNT10/Abstracts/Merkle/index.html.

2323. Ralph C. Merkle, Robert A. Freitas Jr., "Theoretical analysis of a carbon-carbon dimer placement tool for diamond mechanosynthesis," J. Nanosci. Nanotechnol. 3(August 2003):319-324; http://www.rfreitas.com/Nano/DimerTool.htm and http://www.rfreitas.com/Nano/JNNDimerTool.pdf.

2324. Jingping Peng, Robert A. Freitas Jr., Ralph C. Merkle, "Theoretical Analysis of Diamond Mechanosynthesis. Part I. Stability of C2 Mediated Growth of Nanocrystalline Diamond C(110) Surface," J. Comp. Theor. Nanosci. 1(March 2004):62-70; http://www.molecularassembler.com/JCTNPengMar04.pdf.

2325. David J. Mann, Jingping Peng, Robert A. Freitas Jr., Ralph C. Merkle, "Theoretical Analysis of Diamond Mechanosynthesis. Part II. C2 Mediated Growth of Diamond C(110) Surface via Si/Ge-Triadamantane Dimer Placement Tools," J. Comp. Theor. Nanosci. 1(March 2004):71-80; http://www.molecularassembler.com/JCTNMannMar04.pdf.

2326. Danny Hillis, The Connection Machine, MIT Press, Cambridge, MA, 1986.

2327. William A. Goddard III, Tahir Cagin, Stephen P. Walch, "Atomistic design and simulations of nanoscale machines and assembly," Computational Nanotechnology Project, Materials Simulation Center, California Institute of Technology, 1996; http://www.wag.caltech.edu/gallery/nano_comp.html.

2328. Zyvex Corp., "Assembler system design," 21 August 1999; http://www.zyvex.com/Research/SystemDesign.html.

2329. Zyvex Corp., "Molecular Nanotechnology," 7 August 2000; http://www.zyvex.com/Publications/articles/MolecularTech.html.

2330. "3-D Animations for 'Machines Alive': Rotary Assembler," E-SPACES, 1998; http://www.e-spaces.com/broadcast/assembler/index.html; "Rotary Assembler: Movies," http://www.e-spaces.com/broadcast/assembler/asm.mpg.

2331. Forrest Bishop, personal communication to Robert A. Freitas Jr., 1 November 2003.

2332. Animations of MEMS assembly conceptualization; ; http://www.zyvex.com/research/exponential.html. MEMbler$^{\text{TM}}$, see http://www1.zyvex.com:8080/ramgen/videos/mems_adaptive.rm and the RealVideo$^{\text{TM}}$ at http://www1.zyvex.com/videos/mems_adaptive.rm.

2333. Animations of exponential assembly; http://www.zyvex.com/research/exponential.html. Rotapod$^{\text{TM}}$ exponential assembly apparatus, see http://www1.zyvex.com:8080/ramgen/videos/roto_adaptive.rm and the RealVideo$^{\text{TM}}$ at http://www1.zyvex.com/videos/roto_adaptive.rm.

2334. Chris Phoenix, "Design of a Primitive Nanofactory," J. Evol. and Technol. 13(October 2003); http://www.jetpress.org/volume13/Nanofactory.htm . See also: "CRN Research: Current Results — Bootstrapping a Nanofactory," 2003; http://CRNano.org/bootstrap.htm.

2335. Max Glaskin, "Robot builder could 'print' houses," NewScientist.com, 10 March 2004; http://www.newscientist.com/news/news.jsp?id=ns99994764.

2336. Bartosz A. Grzybowski, Michal Radkowski, Christopher J. Campbell, Jessamine Ng Lee, George M. Whitesides, "Self-assembling fluidic machines," Appl. Phys. Lett. 84(8 March 2004):1798-1800; http://scitation.aip.org/getabs/servlet/GetabsServlet?prog=normal&id=APPLAB000084000010001798000001. See also "Self-Assembled Fluidic Machines," Physics News Graphics, 2004; http://www.aip.org/mgr/png/2004/212.htm.

2337. Mike Treder, "Talking the Talk," Center for Responsible Nanotechnology, 10 March 2004; http://crnano.typepad.com/crnblog/2004/03/usc_conference_.html.

2338. Robert A. Freitas Jr., "A simple tool for positional diamond mechanosynthesis, and its method of manufacture," United States Provisional Patent No. 60/543,802, filed 11 February 2004.

2339. Whitney A. Hastings, Mike Labarre, Anand Viswanathan, Stephen Lee, David Sparks, Tony Tran, Jason Nolin, Rob Curry, Michael David, Stanley Huang, Jackrit Suthakorn, Yu Zhou, Gregory S. Chirikjian, "A minimalist parts manipulation system for a self-replicating electromechanical circuit," Department of Mechanical Engineering, Johns Hopkins University, April 2004; http://www.niac.usra.edu/files/studies/final_report/pdf/880Chirikjian.pdf.

2340. Jin Seob Kim, Art Rivera, Danielle Soya, Danny Dokko, Landon Unninayar, Mohammed Ramadon, Robynn Denzene, Zain Syed, Yu Zhou, Jackrit Suthakorn, Gregory S. Chirikjian, "Construction of a prototype of self-replicating electromechanical intelligence," Department of Mechanical Engineering, Johns Hopkins University, April 2004; http://www.niac.usra.edu/files/studies/final_report/pdf/880Chirikjian.pdf.

2341. Jackrit Suthakorn, Gregory S. Chirikjian, "Toward self-replication of robot control circuitry by self-inspection," Department of Mechanical Engineering, Johns Hopkins University, April 2004; http://www.niac.usra.edu/files/studies/final_report/pdf/880Chirikjian.pdf.

2342. William B. Sherman, Nadrian C. Seeman, "A Precisely Controlled DNA Biped Walking Device," Nano Lett. 4(July 2004):1203-1207. See also: Karen Lurie, "Smallest Robot," ScienCentral News, 15 July 2004; http://www.sciencentral.com/articles/view.php3?type=article&article_id=21839 2303; "A Precisely Controlled DNA Biped," 17 July 2004; http://homepages.nyu.edu/~ws33/

2350. John Mingers, Self-Producing Systems : Implications and Applications of Autopoiesis, Plenum Publishing, New York, 1995; J. Mingers, "An introduction to autopoiesis — implications and applications," Systems Practice 2(1989):159-180.

2351. Randall Whitaker, "Autopoiesis Checklist," 2001; http://www.enolagaia.com/Checklist.html.

2352. Humberto R. Maturana, "The organization of the living: A theory of the living organization," Intl. J. Man-Machine Studies, 7(1975):313-332.

2353. Francisco J. Varela, "A calculus for self-reference," Intl. J. General Systems 2(1975):5-24.

2354. Humberto R. Maturana, Francisco J. Varela, Autopoietic Systems, Univ. of Illinois Biological Computer Lab Report 9.4, Urbana, IL, 1975.

2355. Milan Zeleny, Norbert A. Pierre, "Simulation of self-renewing systems," in Eric Jantsch, Conrad H. Waddington, eds., Evolution and Consciousness: Human Systems in Transition, Addison-Wesley, Reading, MA, 1976.

2356. Humberto R. Maturana, Francisco J. Varela, "Autopoiesis: The Organization of the Living," in Humberto R. Maturana, Francisco J. Varela, Autopoiesis and Cognition: The Realization of the Living, Vol. 42, Boston Studies in the Philosophy of Sciences, D. Riedel Publishing Co., Boston, MA, 1980, pp. 59-138.

2357. Milan Zeleny, ed., Autopoiesis: A Theory of Living Organizations, Vol. 3, North Holland Series in General Systems Research, North-Holland, New York, 1981.

2358. Francisco J. Varela, “Autonomy and autopoiesis,” in G. Roth, H. Schwegler, eds., Self- Organizing Systems, Campus Verlag, Frankfurt, 1981, pp. 14-23.
2359. T. Winograd, F. Flores, Understanding Computers and Cognition, Addison-Wesley, Reading, MA, 1986.
2360. Humberto R. Maturana, Francisco J. Varela, The Tree of Knowledge, Shambhala Publications, Boston, MA, 1987.
2361. S. Vogel, Life’s Devices: The Physical World of Animals and Plants, Princeton University Press, Princeton, NJ, 1988.
2362. Francisco J. Varela, Paul Bourgine, eds., Toward a Practice of Autonomous Systems: Proceedings of the First European Conference on Artificial Life, MIT Press, Cambridge, MA, 1992.
2363. G. Kampis, “Life-like computing beyond the machine metaphor,” in R. Paton, ed., Computing with Biological Metaphors, Chapman and Hall, London, 1994.
2364. Barry McMullin, “Computational autopoiesis: the original algorithm,” Working Paper 97-01-001, Santa Fe Institute, Santa Fe, NM, January 1997; http://www.santafe.edu/sfi/publications/Working-P< 97-01-001>.
2365. Barry McMullin, “SCL: An artificial chemistry in Swarm,” Working Paper 97-01-002, Santa Fe Institute, Santa Fe, NM, 1997.
2366. Randall Whitaker, Encyclopaedia Autopoietica: An Annotated Lexical Compendium on Autopoiesis and Enaction, 2001; http://www.informatik.umu.se/~rwhit/EAIntro.html or http://www.informatik.umu.se/%7Erwhit/EA.html.
2367. Barry McMullin, “Some remarks on autocatalysis and autopoiesis,” Technical Report No. bmcm-9901, presented at workshop, Closure: Emergent Organizations and their Dynamics, 3-5 May 1999, University of Ghent, Belgium; http://www.eeng.dcu.ie/~alife/bmcm9901/.
2368. Barry McMullin, Dominique Gross, “Towards the implementation of evolving autopoietic artificial agents,” in J. Kelemen, P. Sosik, eds., Advances in Artificial Life, Proceedings of the 6th European Conference, Springer; Technical Report No. bmcm-ecal-2001, presented at ECAL, Prague, Czech Republic, September 2001; http://www.eeng.dcu.ie/~alife/bmcm-ecal-2001/. See also Barry McMullin’s artificial life work “DCU ALife Lab” describing basic autopoietic agents in Virtual Chemistries; http://www.eeng.dcu.ie/~alife/Research.html.
2369. F.J. Varela, J. Goguen, “The arithmetic of closure,” J. Cybernetics 8(1978):291-324.
2370. Francisco J. Varela, Principles of Biological Autonomy, Elsevier North-Holland, New York, 1979.
2371. Jerry L.R. Chandler, Gertrudis van de Vijver, eds., Closure: Emergent Organizations and their Dynamics, Annals N.Y. Acad. Sci. 901(2000).
2372. A.A. Bogdanov, Tektologia: Vseobschaya Organizatsionnaya Nauka, Z.I. Grschebin Verlag, Berlin, 1922; reprinted as: A.A. Bogdanov, Essays in the Universal Organizational Science, InterSystems Publishers, 1980. (Translated into English by G. Gorelik).
2373. Walter Fontana, “The barrier of objects: From dynamical systems to bounded organizations,” Santa Fe Institute Working Paper 96-05-035; http://www.santafe.edu/sfi/publications/Working-Papers/96-05-035.ps.
2374. P.O. Luksha, “The firm as a self-reproducing system,” ISSS’03 Conference Proceedings, Crete, Greece, 2003; http://www.systemicbusiness.org/digests/sabi2003/2003_ISSS_47th_069_Luksha.pdf or http://www.unizar.es/sociocybernetics/congresos/CORFU/papers/luksha.pdf.
2375. D. Richardson, “Continuous self-reproduction,” J. Comput. Syst. Sci. 12(1976):6-12.
2376. B. Goodwin, “A relational or field theory of reproduction and its evolutionary implications,” in M.W. Ho, P.T. Saunders, eds., Beyond Neo-Darwinism, Academic Press, London, 1984, pp. 219-241.
2377. G. Kampis, V. Csanyi, “Life, self-reproduction and information: Beyond the machine metaphor,” J. Theor. Biol. 148(1991):17-32.
2378. George Kampis, Self-Modifying Systems in Biology and Cognitive Science, Pergamon Press, Oxford, 1991.
2379. Arantza Etxeberria, “Embodiment of natural and artificial systems,” in G. van de Vijver, S. Salthe, eds., Proc. Intl. Seminar on Evolutionary Systems, Vienna, 1995.
2380. Luis M. Rocha, “Eigenbehavior and symbols,” Systems Research 12(1996):371-384; http://www.c3.lanl.gov/~rocha/sr.html.
2381. Luis M. Rocha, “Selected self-organization and the semiotics of evolutionary systems,” in S. Salthe, G. Van de Vijver, M. Delpos, eds., Evolutionary Systems: The Biological and Epistemological Perspectives on Selection and Self-Organization, Kluwer Academic Publishers, 1998, pp. 341-358; http://wwwc3.lanl.gov/~rocha/ises.html or http://wwwc3.lanl.gov/~rocha/ps/ises.pdf.
2382. Howard H. Pattee, “Evolving self-reference: matter, symbols, and semantic closure,” Communication and Cognition — Artificial Intelligence 12(1995):9-27 (Special Issue on Self-Reference in Biological and Cognitive Systems).
2383. Howard H. Pattee, “Cell psychology: an evolutionary approach to the symbol-matter problem,” Cognition and Brain Theory 5(1982):325-341.
2384. Luis M. Rocha, “Artificial semantically closed objects,” Communication and Cognition — Artificial Intelligence 12(1995):63-90 (Special Issue on Self-Reference in Biological and Cognitive Systems); http://www.c3.lanl.gov/~rocha/tilsccai.html.
2385. Jon Umerez, “Semantic closure: a guiding notion to ground Artificial Life,” in F. Moran, A. Moreno, J.J. Merelo, P. Chacon, eds., Advances in Artificial Life, Springer-Verlag, New York, 1995, pp. 77-94.
2386. Tatsuya Nomura, “Formal description of autopoiesis for analytic models of life and social systems,” in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 15-18; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub358.pdf.
2387. Barry McMullin, “John von Neumann and the evolutionary growth of complexity: looking backwards, looking forwards…” in Artificial Life VII, Proceedings of the Seventh International Conference on Artificial Life, MIT Press, Cambridge, MA, 2000, pp. 467-476; http://www.eeng.dcu.ie/~alife/bmcm-2000-01/; also published in Artificial Life 6(Fall 2000):347-361; http://www.eeng.dcu.ie/~alife/bmcm-alj-2000/.
2388. Pavel O. Luksha, “Formal definition of self-reproductive systems,” in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 414-417; http://parallel.hpc.unsw.edu.au/complex/alife8/proceedings/sub2783.pdf.
2389. Alexei A. Sharov, “Self-reproducing systems: structure, niche relations and evolution,” BioSystems 25(1991):237-249; http://www.gypsymoth.ento.vt.edu/~sharov/biosem/petri/petri.html (summary) or http://www.gypsymoth.ento.vt.edu/~sharov/pdf/selfrep.pdf (paper).
2390. L. Lofgren, “Kinematic and tessellation models of self-repair,” in E.E. Bernard, M.A. Dare, eds., Biological Prototypes and Synthetic Systems, Vol. 1, Plenum Press, New York, 1962, pp. 342-369.
2391. “Chapter IX. On Learning and Self-Reproducing Machines,” in Norbert Wiener, Cybernetics, 2nd Edition, MIT Press, Cambridge, MA, 1965, pp. 169-180.
2392. G. Nicolis, I. Prigogine, Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order Through Fluctuations, John Wiley & Sons, New York, 1977.
2393. James Grier Miller, Living Systems, McGraw-Hill Book Company, New York, 1978.
2394. Robert A. Freitas Jr., “A general theory of living systems,” Analog 100(March 1980):61-75.
2395. Stuart A. Kauffman, At Home in the Universe: The Search for the Laws of Self-Organization and Complexity, Oxford University Press, New York, 1995.
2396. Stuart A. Kauffman, The Origins of Order: Self-Organization and Selection in Evolution, Oxford University Press, New York, 1993.
2397. Freeman J. Dyson, Origins of Life, Cambridge University Press, New York, 1999.
2398. Daniel Segre, Dafna Ben-Eli, Doron Lancet, “Compositional genomes: prebiotic information transfer in mutually catalytic noncovalent assemblies,” Proc. Natl. Acad. Sci. (USA) 97(11 April 2000):4112-4117; http://www.pnas.org/cgi/content/full/97/8/4112. Daniel Segre, “Inheritance without biopolymers in a computer model for primordial evolution,” Krasnow Institute, George Mason University, 1999; http://www.gmu.edu/departments/krasnow/abstracts_frames/abs99/segr9907.htm (Abstract).
2399. Kevin J. Gaston, Robert M. May, “Taxonomy of taxonomists,” Nature 356(26 March 1992):281-282.
2400. Hideaki Suzuki, Naoaki Ono, Kikuo Yuta, “Several necessary conditions for the evolution of complex forms of life in an artificial environment,” Artif. Life 9(Spring 2003):153-174.
2401. Kenneth O. Stanley, Risto Miikkulainen, “A taxonomy for artificial embryogeny,” Artif. Life 9(Spring 2003):93-130.
2402. Mengly Chean, Jose A.B. Fortes, “A taxonomy of reconfiguration techniques for fault-tolerant processor arrays,” IEEE Computer 23(January 1990):55-69.
2403. Robert N. Brandon, “Adaption explanations: are adaptions for the good of replicators or interactors?” http://students.washington.edu/twelser/evolve.htm.

2404. D.L. Hull, "Individuality and selection," Ann. Rev. Ecol. Syst. 11(1980):311-332.
2405. Barry McMullin, "Replicators Don't!" ECAL'95: Third European Conference on Artificial Life, 1995; http://www.eeng.dcu.ie/~alife/ecal95/rpl-l2h/rpl-l2h.html.
2406. Barbara Webb, Thomas R. Consi, eds., Biorobotics, AAAI Press, 2001.
2407. Joseph Ayers, Joel L. Davis, Alan Rudolph, eds., Neurotechnology for Biomimetic Robots, MIT Press, Cambridge, MA, 2002.
2408. Roger Quinn, Biologically Inspired Robotics Lab, Case Western Reserve University, 2003; http://biorobots.cwru.edu/. See also: Roger Quinn Biologically Inspired Micro-Robots; http://www.darpa.mil/mto/drobotics/summaries/00overviews/CaseWestern.html.
2409. Yoseph Bar-Cohen, Cynthia Breazeal, eds., Biologically Inspired Intelligent Robots, Monograph Vol. PM122, SPIE Press (Society of Photo-optical Instrumentation Engineers), 2003.
2410. Biologically Inspired Robotics Group (BIRG), EPFL; http://lslwww.epfl.ch/birg/.
2411. E. Szathmary, J. Maynard Smith, "The origin of genetic systems," Abstracta Botanica 17(1993):197-206.
2412. Eors Szathmary, "A classification of replicators and lambda-calculus models of biological organization," Proc. R. Soc. Lond. B 260(1995):279-286.
2413. E. Szathmary, J. Maynard Smith, "The major evolutionary transitions," Nature 374(1995):227-232.
2414. John Maynard Smith, Eors Szathmary, The Major Transitions in Evolution, Oxford University Press, New York, 1995.
2415. Eors Szathmary, John Maynard Smith, "From replicators to reproducers: the first major transitions leading to life," J. Theor. Biol. 187(1997):555-571.
2416. Eors Szathmary, "Chemes, genes, memes: a revised classification of replicators," Lectures on Math. Life Sci. 26(1999):1-10.
2417. Eors Szathmary, "The evolution of replicators," Phil. Trans. R. Soc. Lond. B 355(2000):1669-1676.
2418. H.H. Pattee, "The recognition of hereditary order in primitive chemical systems," in S.W. Fox, ed., The Origins of Prebiological Systems and of their Molecular Matrices, Academic Press, New York, 1965, pp. 388-389.
2419. A. Butlerow, "Formation synthetique d'une substance sucr'ee," C. R. Acad. Sci. 53(1861):145-147.
2420. G. Wachtershauser, "Life in a ligand sphere," Proc. Nat. Acad. Sci. (USA) 91(1994):4283-4287.
2421. Andrew D. Ellington, Matthew Levy, "Comparative biology of replicators," Oral Presentation, Second Astrobiology Science Conference, NASA/AMES Research Center, 7-11 April 2002; http://www.astrobiology.com/asc2002/abstract.html?ascid=132 (abstract).
2422. T. Cavalier-Smith, "Membrane heredity, symbiogenesis, and the multiple origins of algae," in M. Kato, Y. Doi, eds., Biodiversity and Evolution, National Science Museum Foundation, Tokyo, 1995, pp. 75-114.
2423. M. Pagel, D.C. Krakauer, "Prions and the new molecular phenetics," Trends Ecol. Evol. 11(1996):487-488.
2424. M.M. Patino, J.J. Liu, J.R. Glover, S. Lindquist, "Support for the prion hypothesis for the inheritance of a phenotypic trait in yeast," Science 273(1996):622-626.
2425. M.F. Tuite, S.L. Lindquist, "Maintenance and inheritance of yeast prions," Trends Genet. 12(1996):467-471.
2426. T.M. Sonneborn, "The differentiation of cells," Proc. Natl. Acad. Sci. (USA) 51(1964):915-929.
2427. Daniel Segre, Doron Lancet, Ora Kedem, Yitzhak Pilpel, "Graded autocatalysis replication domain (GARD): kinetic analysis of self-replication in mutually catalytic sets," Orig. Life Evol. Biosphere 28(1998):501-514; http://genetics.med.harvard.edu/~dsegre/Segre_etal_OLEB_1998.pdf.
2428. Daniel Segre, Dafna Ben-Eli, David W. Deamer, Doron Lancet, "The lipid world," Orig. Life Evol. Biosphere 31(2001):119-145; http://genetics.med.harvard.edu/~dsegre/Segre_etal_OLEB_2000_Lipid_World.pdf.
2429. P. Hogeweg, "On searching generic properties of non generic phenomena: an approach to bioinformatic theory formation," in C. Adami, R.K. Belew, H. Kitano, C.E. Taylor, eds., Artificial Life VI, MIT Press, Cambridge, MA, 1998, pp. 285-294.
2430. M. Sipper, E. Sanchez, D. Mange, M. Tomassini, A. Pérez-Uribe, A. Stauffer, "The POE model of bio-inspired hardware systems: A short introduction," in J.R. Koza, K. Deb, M. Dorigo, D.B. Fogel, M. Garzon, H. Iba, R.L. Riolo, eds., Genetic Programming 1997: Proceedings of the Second Annual Conference, Morgan Kaufmann, San Francisco, CA, 1997, pp. 510-511; http://lslwww.epfl.ch/~moshes/poe.html.
2431. M. Sipper, E. Sanchez, D. Mange, M. Tomassini, A. Pérez-Uribe, A. Stauffer, "A phylogenetic, ontogenetic, and epigenetic view of bio-inspired hardware systems," IEEE Trans. Evol. Comp. 1(April 1997):83-97.
2432. E. Sanchez, D. Mange, M. Sipper, M. Tomassini, A. Pérez-Uribe, A. Stauffer, "Phylogeny, ontogeny, and epigenesis: three sources of biological inspiration for softening hardware," in T. Higuchi, M. Iwata, W. Liu, eds., Proceedings of The First International Conference on Evolvable Systems: from Biology to Hardware (ICES96), Lecture Notes in Computer Science, Springer-Verlag, Heidelberg, Vol. 1259, 1997, pp. 35-54.
2433. M. Sipper, E. Sanchez, D. Mange, M. Tomassini, A. Pérez-Uribe, A. Stauffer, "The POE model of bio-inspired hardware systems': http://www.cs.bgu.ac.il/~sipper/poe.html. See also website at http://www.poetictissue.org.
2434. Gianluca Tempesti, Daniel Roggen, Eduardo Sanchez, Yann Thoma, Richard Canham, Andy Tyrrell, Juan-Manuel Moreno, "A POEtic architecture for bio-inspired hardware," in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 111-115; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub3567.pdf.
2435. Karl F. Bohringer, Ronald S. Fearing, Ken Y. Goldberg, "Chapter 55. Microassembly," in Shimon Y. Nof, ed., Handbook of Industrial Robotics, Second Edition, John Wiley and Sons, New York, 1999, pp. 1045-1066; http://www.ee.washington.edu/faculty/karl/Publications/PS/HBIR2.ps.gz.
2436. Barmeshwar Vikramaditya, Bradley J. Nelson, "Visually guided microassembly using optical microscopes and active vision techniques," Proc. 1997 IEEE International Conference on Robotics and Automation, 20-25 April 1997, IEEE Robotics and Automation Society, pp. 3172-3177.
2437. J.T. Feddema, R.W. Simon, "CAD-driven microassembly and visual servoing," Proc. IEEE Intl. Conf. on Robotics and Automation (ICRA), May 1998.
2438. A.E. Quaid, R.L. Hollis, "Cooperative 2-DOF robots for precision assembly," Proc. IEEE Intl. Conf. on Robotics and Automation (ICRA), April 1996.
2439. Wolfgang Zesch, "Multi-degree-of-freedom micropositioning using stepping principles," Ph.D. Thesis, ETH-Diss 12318, EPFL, Swiss Federal Institute of Technology, Lausanne, 1997.
2440. G. Danuser, I. Pappas, B. Vogeli, W. Zesch, J. Dual, "Manipulation of microscopic objects with nanometer precision: Potentials and limitations in nano-robot design," Intl. J. Robotics Res. (1997), submitted for publication.
2441. MRSI International; company acquired in 2002 by Newport Corp., Irvine, CA; http://www.newport.com.
2442. Chang-Jin Kim, Albert P. Pisano, Richard S. Muller, Martin G. Lim, "Polysilicon microgripper," Sensors and Actuators A 33(1992):221-227. See also: "Silicon-processed overhanding microgripper," J. Microelectromech. Syst. 1(March 1992):31-36 and "Design, fabrication and testing of a polysilicon microgripper," Microstructures, Sensors, and Actuators, ASME, New York, DSC-19(1990):99-109.
2443. C. Keller, R.T. Howe, "Nickel-filled hexsil thermally actuated tweezers," Transducers — Digest of Intl. Conf. on Solid-State Sensors and Actuators, Stockholm, June 1992.
2444. C. Keller, R.T. Howe, "Hexsil tweezers for teleoperated micro-assembly," Proc. IEEE Workshop on Micro Electro Mechanical Systems (MEMS), Nagoya, Japan, January 1997, pp. 72-77.
2445. K.S.J. Pister, M.W. Judy, S.R. Burgett, R.S. Fearing, "Microfabricated hinges," Sensors and Actuators A 33(1992):249-256.
2446. Elisabeth Smela, Olle Inganas, Ingemar Lundstrom, "Controlled folding of micrometer-size structures," Science 268(23 June 1995):1735-1738. See also: Yingkai Liu, Hyo Suk Oh, Elisabeth Smela, "Micro-origami: Fabrication of self-folding microstructures," http://www.enme.umd.edu/news/November01/micro-origami.pdf.

2447. Vladimir A. Aksyuk, David J. Bishop, “Self-assembling micro-mechanical device,” United States Patent No. 5,994,159, 30 November 1999; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,994,159.WKU.&OS=PN/5,994,159.

2448. S.T. Brittain, O.J.A. Schueller, H. Wu, S. Whitesides, G.M. Whitesides, “Microorigami: fabrication of small, three-dimensional, metallic structures,” J. Phys. Chem. B 105(2001):347-350.

2449. A. Singh et al, “Batch transfer of microstructures using flip-chip solder bump bonding,” Transducers — Digest of Intl. Conf. on Solid-State Sensors and Actuators, Chicago, June 1997.

2450. H.J. Yeh, J.S. Smith, “Fluidic self-assembly of microstructures and its application to the integration of GaAs on Si,” Proc. IEEE Workshop on Micro Electro Mechanical Systems (MEMS), Oiso, Japan, 1994, pp. 279-284; H.J. Yeh, J.S. Smith, “Integration of GaAs vertical cavity surface-emitting laser on Si by substrate removal,” Appl. Phys. Lett. 64(1994):1466-1468.

2451. S. Pestka, B.L. Daugherty, V. Jung, K. Hotta, R.K. Pestka, “Anti-mRNA: specific inhibition of translation of single mRNA molecules,” Proc. Natl. Acad. Sci. (USA) 81(December 1984):7525-7528.

2452. Eliezer S. Yudkowsky, personal communication to Robert A. Freitas Jr., 11 August 2003.

2453. “BattleBots Technical Regulations,” Version 3.1, BattleBots Inc., 22 April 2003; http://www.battlebots.com/download/BattleBots_Tech_Regs_v3.1.pdf.

2454. BattleBots website; http://www.battlebots.com.

2455. “The Sorcerer’s Apprentice,” segment in animated movie Fantasia, Walt Disney Pictures, 1941; http://www.filmsite.org/fant2.html. Musical score at http://www.cuttime.com/sorcerer.htm.

2456. Johann Wolfgang von Goethe, “The Sorcerer’s Apprentice,” 1779. Translation by Edgar A. Bowring, 1853, http://www.fln.vcu.edu/goethe/zauber_e.html; translation by W.E. Aytoun, T. Martin, 1859, http://www.fln.vcu.edu/goethe/zauber_e5.html; translation by Paul Dyrsen, 1878, http://www.fln.vcu.edu/goethe/zauber_e4.html; translation by Edwin Zeydel, 1955, http://www.fln.vcu.edu/goethe/zauber_e3.html.

2457. Lucian of Samosata (Lucianus), “Philopseudes” (The Lover of Lies) 34-36, 150 A.D.; original Greek text http://www.grammatika.150m.com/lucian-philopseudes.htm and Dutch translation at http://home.tiscali.be/be047225/cycade/tovll.htm.

2458. V.V. Kuvshinov, K. Koivu, A. Kanerva, E. Pehu, “Molecular control of transgene escape from genetically modified plants,” Plant Sci. 160(5 February 2001):517-522; S. Smyth, G.G. Khachatourians, P.W. Phillips, “Liabilities and economics of transgenic crops,” Nat. Biotechnol. 20(June 2002):537-541.

2459. J. Kaiser, “Biotechnology. USDA to commercialize ‘terminator’ technology,” Science 289(4 August 2000):709-710; Rob Edwards, “End of the germ line,” New Scientist, 28 March 1998; http://www.newscientist.com/hottopics/gm/gm.jsp?id=21274200.

2460. H. Shand, “Terminator no solution to gene flow,” Nat. Biotechnol. 20(August 2002):775-776.

2461. Johann P. Schernthaner, Steven F. Fabijanski, P.G. Arnison, M. Racicot, L.S. Robert, “Control of seed germination in transgenic plants based on the segregation of a two-component genetic system,” Proc. Natl. Acad. Sci. (USA) (9 May 2003) [epub ahead of print]; http://www.pnas.org/cgi/reprint/1036833100. See also: Randolph E. Schmid, “Biotech Crops’ Crossbreeding Targeted,” Associated Press, 5 May 2003; http://story.news.yahoo.com/news?tmpl=story&cid=624&ncid=624&e=2&u=/ap/20030505/ap_on_sc/biotech_crops.

2462. D.E. Post, F.R. Khuri, J.W. Simons, E.G. Van Meir, “Replicative oncolytic adenoviruses in multimodal cancer regimens,” Hum. Gene Ther. 14(1 July 2003):933-946; A. Kanerva, K.R. Zinn, T.R. Chaudhuri, J.T. Lam, K. Suzuki, T.G. Uil, T. Hakkarainen, G.J. Bauerschmitz, M. Wang, B. Liu, Z. Cao, R.D. Alvarez, D.T. Curiel, A. Hemminki, “Enhanced therapeutic efficacy for ovarian cancer with a serotype 3 receptor-targeted oncolytic adenovirus,” Mol. Ther. 8(September 2003):449-458.

2463. W.N. Reynolds, J.E. Pearson, S. Ponce-Dawson, “Dynamics of self-replicating patterns in reaction diffusion systems,” Phys. Rev. Lett. 72(1994):2797-2800.

2464. O. White et al, “Genome sequence of the radioresistant bacterium Deinococcus radiodurans R1,” Science 286(19 November 1999):1571-1577.

2465. S.N. Peterson, C.C. Bailey, J.S. Jensen, M.B. Borre, E.S. King, K.F. Bott, C.A. Hutchison 3rd, “Characterization of repetitive DNA in the Mycoplasma genitalium genome: possible role in the generation of antigenic variation,” Proc. Natl. Acad. Sci. (USA) 92(5 December 1995):11829-11833; http://www.pnas.org/cgi/reprint/92/25/11829.

2466. Homer Jacobson, “The information content of mechanisms and circuits,” Information and Control 2(1959):285-296.

2467. Homer Jacobson, “Information, reproduction and the origin of life,” Amer. Sci. 43(1955):119-127.

2468. Marcel Golay, “Reflections of a communications engineer,” Anal. Chem. 33(June 1961):23.

2469. Ramanujan S. Hegde, J.A. Mastrianni, M.R. Scott, K.A. DeFea, P. Tremblay, M. Torchia, S.J. DeArmond, S.B. Prusiner, V.R. Lingappa, “A transmembrane form of the prion protein in neurodegenerative disease,” Science 279(6 February 1998):827-834.

2470. Stanley B. Prusiner, “The prion diseases,” Sci. Amer. 272(January 1995):48-57.

2471. H. Toyoda, M. Kohara, Y. Kataoka, T. Suganuma, T. Omata, N. Imura, A. Nomoto, “Complete nucleotide sequences of all three poliovirus serotype genomes. Implication for genetic relationship, gene function and antigenic determinants,” J. Mol. Biol. 174(25 April 1984):561-585. See also: “Genome of human poliovirus type 1 (Mahoney strain),” http://web.ncbi.nlm.nih.gov:2441/entrez/query.fcgi?cmd=Retrieve&db=nucleotide&list_uids=61236&dopt=GenBank.

2472. “Ebola virus complete sequence,” http://bt.swmed.edu/genomesOther/ebolavirus.txt.

2473. Myles Axton, “Regulation of a runaway replicator,” at: http://web.uct.ac.za/microbiology/ebola-re.html.

2474. Marco A. Marra, et al, “The genome sequence of the SARS-associated coronavirus,” Science 300(30 May 2003):1399-1404; http://www.sciencemag.org/cgi/content/abstract/1085953v1 (abstract) and http://www.sciencemag.org/cgi/rapidpdf/1085953v1 (paper). See also: “SARS coronavirus, complete genome”; http://web.ncbi.nlm.nih.gov:2441/entrez/viewer.fcgi?val=NC_004718.

2475. “Bacteriophage T4, complete genome,” NCBI nt database, NIH; http://lgsun.grc.nia.nih.gov/cgi-bin/pro21?sname=J0221H11-3.

2476. Ralph C. Merkle, “Some links to the (Robert Morris, Jr.) internet worm incident of 1988”; http://www.zyvex.com/nanotech/worm.html.

2477. E. Waters, M.J. Hohn, I. Ahel, D.E. Graham, M.D. Adams, M. Barnstead, K.Y. Beeson, L. Bibbs, R. Bolanos, M. Keller, K. Kretz, X. Lin, E. Mathur, J. Ni, M. Podar, T. Richardson, G.G. Sutton, M. Simon, D. Soll, K.O. Stetter, J.M. Short, M. Noordewier, “The genome of Nanoarchaeum equitans: Insights into early archaeal evolution and derived parasitism,” Proc. Natl. Acad. Sci. (USA) 100(28 October 2003):12984-12988. See also: “Diversa Sequences Smallest Genome to Date, Nanoarchaeum equitans,” GenomeWeb News, 14 October 2003; http://www.genomeweb.com/articles/view-article.asp?Article=2003101482528.

2478. “Mol-Biol 4 Masters: Plants”; http://www.mol-biol4masters.com/plants.html.

2479. R.D. Fleischmann, M.D. Adams, O. White, R.A. Clayton, E.F. Kirkness, A.R. Kerlavage, C.J. Bult, J.F. Tomb, B.A. Dougherty, J.M. Merrick et al, “Whole-genome random sequencing and assembly of Haemophilus influenzae Rd,” Science 269(28 July 1995):496-512.

2480. F.R. Blattner, G. Plunkett 3rd, C.A. Bloch, N.T. Perna, V. Burland, M. Riley, J. Collado-Vides, J.D. Glasner, C.K. Rode, G.F. Mayhew, J. Gregor, N.W. Davis, H.A. Kirkpatrick, M.A. Goeden, D.J. Rose, B. Mau, Y. Shao, “The complete genome sequence of Escherichia coli K-12,” Science 277(5 September 1997):1453-1474.

2481. “Systematic Sequencing Table: *Saccharomyces cerevisiae* chromosome statistics and retrieval options,” Saccharomyces Genome Database (SGD$^{\text{TM}}$) project , 2003; http://genome-www.stanford.edu/Saccharomyces/chromosomes.shtml.

2482. The Arabidopsis Genome Initiative, “Analysis of the genome sequence of the flowering plant Arabidopsis thaliana,” Nature 408(14 December 2000):796-815; Arabidopsis Genome Initiative (AGI), http://www.arabidopsis.org/agi.html.

2483. “Genome Sizes,” 9 October 2002; http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/G/GenomeSizes.html.

2484. M.D. Adams et al, “The genome sequence of *Drosophila melanogaster*,” Science 287(24 March 2000):2185-2195; http://www.sciencemag.org/cgi/content/full/287/5461/2185?ijkey=S7.54upPrNbe.

2485. P.J. Lea, R.C. Leegods, eds., Plant Biochemistry and Molecular Biology, John Wiley & Sons, Ltd., 1993.
2486. Z. Xuan, J. Wang, M.Q. Zhang, "Computational comparison of two mouse draft genomes and the human golden path," Genome Biol. 4(2003):R1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=12537546. See also: R.H. Waterston et al, "Initial sequencing and comparative analysis of the mouse genome" Nature 420(5 December 2002):520-562.
2487. E.S. Lander et al., "Initial sequencing and analysis of the human genome," Nature 409(15 February 2001):860-921; http://www.ornl.gov/TechResources/Human_Genome/posters/chromosome/faqs.html.
2488. K. Arumuganathan, E.D. Earle, "Nuclear DNA content of some important plant species," Plant Mol. Biol. Rep. 9(1991):208-219. See Table I, "Nuclear DNA content of a number of important plant species as determined by flow cytometry," pp. 211-215; http://www.nal.usda.gov/pgdic/tables/nucdna.html.
2489. "Which organism has the highest amount of DNA?" Question Number: b01010d, ScienceNet, 2003; http://www.sciencenet.org.uk/database/Biology/0109/b01010d.html.
2490. C.T. Friz, "The biochemical composition of the free-living amoebae *Chaos chaos*, *Amoeba dubia*, and *Amoeba proteus*," Comp. Biochem. Physiol. 26(1968):81-90; T.J. Byers, "Molecular biology of DNA in *Acanthamoeba*, *Amoeba*, *Entamoeba*, and *Naegleria*," Intl. Rev. Cytol. 99(1986):311-341.
2491. W.-H. Li, Molecular Evolution, Sinauer Associates, Inc., Sunderland, MA, 1997.
2492. Edward R. Winstead, "Sizing up genomes: Amoeba is king," Genome News Network, 12 February 2001; http://gnn.tigr.org/articles/02_01/Sizing_genomes.shtml.
2493. T. Ryan Gregory, "Animal Genome Size Database"; http://www.genomesize.com/summary.htm.
2494. M. Kidwell, "Lateral transfer in natural populations of eukaryotes," Ann. Rev. Genet. 27(1993):235-256.
2495. M. Syvanen, "Horizontal gene transfer: evidence and possible consequences," Ann. Rev. Genet. 28(1994):237-261.
2496. M. Syvanen, C.I. Kado, Horizontal Gene Transfer, Chapman and Hall, London, 1998.
2497. Jeffrey G. Lawrence, "Gene transfer and minimal genome size," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel1lawrence.htm.
2498. A.P. McCaffrey, H. Nakai, K. Pandey, Z. Huang, F.H. Salazar, H. Xu, S.F. Wieland, P.L. Marion, M.A. Kay, "Inhibition of hepatitis B virus in mice by RNA interference," Nat. Biotechnol. (12 May 2003) [epub ahead of print]; Karla Gale, "RNA interference inhibits HBV replication in vivo," Reuters Health, 16 May 2003; http://www.reutershealth.com/archive/2003/05/16/professional/links/20030516scie003.html. See also: A. Shlomai, Y. Shaul, "Inhibition of hepatitis B virus expression and replication by RNA interference," Hepatology 37(April 2003):764-770; K. Hamasaki, K. Nakao, K. Matsumoto, T. Ichikawa, H. Ishikawa, K. Eguchi, "Short interfering RNA-directed inhibition of hepatitis B virus replication," FEBS Lett. 543(22 May 2003):51-54.
2499. Luis M. Rocha, "Contextual genetic algorithms: evolving developmental rules," in F. Moran, A. Moreno, J.J. Merelo, P. Chacon, eds., Advances in Artificial Life, Springer-Verlag, New York, 1995, pp. 368-382; http://wwwc3.lanl.gov/~rocha/e95_abs.html.
2500. B. Blum, N. Bakalara, L. Simpson, "A model for RNA editing in kinetoplastid mitochondria: 'guide' RNA molecules transcribed from maxicircle DNA provide the edited information," Cell 60(26 January 1990):189-198; N.R. Sturm, L. Simpson, "Kinetoplast DNA minicircles encode guide RNAs for editing of cytochrome oxidase subunit III mRNA," Cell 61(1 June 1990):879-884; T.L. Horton, L.F. Landweber, "Rewriting the information in DNA: RNA editing in kinetoplastids and myxomycetes," Curr. Opin. Microbiol. 5(December 2002):620-626.
2501. M. Schaub, W. Keller, "RNA editing by adenosine deaminases generates RNA and protein diversity," Biochimie 84(August 2002):791-803.
2502. K. Stuart, A.K. Panigrahi, "RNA editing: complexity and complications," Mol. Microbiol. 45(August 2002):591-596.
2503. R. Benne, J. Van den Burg, J.P. Brakenhoff, P. Sloof, J.H. Van Boom, M.C. Tromp, "Major transcript of the frameshifted coxII gene from trypanosome mitochondria contains four nucleotides that are not encoded in the DNA," Cell 46(12 September 1986):819-826.
2504. Robert Benne, ed., RNA Editing: The Alteration of Protein Coding Sequences of RNA, Ellis Horwood Ltd., 1993.
2505. S.D. Seiwert, K. Stuart, "RNA editing: transfer of genetic information from gRNA to precursor mRNA in vitro," Science 266(7 October 1994):114-117.
2506. A.M. Estevez, L. Simpson, "Uridine insertion/deletion RNA editing in trypanosome mitochondria — a review," Gene 240(29 November 1999):247-260.
2507. L. Simpson, S. Sbicego, R. Aphasizhev, "Uridine insertion/deletion RNA editing in trypanosome mitochondria: a complex business," RNA 9(March 2003):265-276.
2508. H. Lomeli, J. Mosbacher, T. Melcher, T. Hoger, J.R. Geiger, T. Kuner, H. Monyer, M. Higuchi, A. Bach, P.H. Seeburg, "Control of kinetic properties of AMPA receptor channels by nuclear RNA editing," Science 266(9 December 1994):1709-1713.
2509. Hiroki Sayama, personal communication to Robert A. Freitas Jr., 22 October 2003.
2510. G. Paun, "Computing with membranes," J. Comp. Syst. Sci. 61(2000):108-143.
2511. A. Calinescu, J. Efstathiou, S. Sivadasan, J. Schirn, L. Huaccho Huatuco, "Complexity in manufacturing: an information theoretic approach," Proc. Intl. Conf. on Complexity and Complex Systems in Industry, 19-20 September 2000, The University of Warwick, 2000, pp. 30-44; http://www.robots.ox.ac.uk/~manufsys/warwick_calinescu.ps. See Manufacturing Systems Group website at http://www.robots.ox.ac.uk/~manufsys/.
2512. Michael New, Charles Blackwell, Kagan Tumer, Dimitris Stassinopoulos, "Who or what? Replication of identities or functions," Poster Presentation, Second Astrobiology Science Conference, NASA/AMES Research Center, 7-11 April 2002; http://www.astrobiology.com/asc2002/abstract.html?ascid=311.
2513. K.N. Laland, J. Odling-Stone, M.W. Feldman, "Niche construction, biological evolution, and cultural change," Behav. Brain Sci. 23(2000):131-175.
2514. B. Adams, H. Lipson, "A universal framework for self replication," 7th European Conference on Artificial Life (ECAL 2003), 14-17 September 2003, Dortmund, Germany, 2003, pp. 1-9; http://ls11-www.cs.uni-dortmund.de/people/ziegler/ecal2003/accepted/118.html (abstract) and http://www.mae.cornell.edu/lipson/papers/selfrep.pdf (paper).
2515. Rok Sosic, Robert R. Johnson, "Computational properties of self-reproducing growing automata," BioSystems 36(1995):7-17; http://www.cit.gu.edu.au/~sosic/abstracts/biosystems95.html (abstract) and http://www.cit.gu.edu.au/~sosic/papers/biosystems95.ps.Z (paper).
2516. Wil McCarthy, Hacking Matter: Levitating Chairs, Quantum Mirages, and the Infinite Weirdness of Programmable Atoms, Basic Books, New York, 2003.
2517. Jack W. Szostak, "Constraints on the sizes of the earliest cells," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel4szostak.htm.
2518. H.V. Chetverina, A.B. Chetverin, "Cloning of RNA molecules in vitro," Nucleic Acids Res. 21(25 May 1993):2349-2353.
2519. D.S. Tawfik, A.D. Griffiths, "Man-made cell-like compartments for molecular evolution," Nat. Biotechnol. 16(July 1998):652-656.
2520. E. Olavi Kajander, Mikael Bjorklund, Neva Ciftcioglu, "Suggestions from observations on nanobacteria isolated from blood," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel2kajander.htm.
2521. James L. Van Etten, "Can large dsDNA-containing viruses provide information about the minimal genome size required to support life?" in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel2vanetten.htm.
2522. H. Chen, I.M. Keseler, L.J. Shimkets, "Genome size of Myxococcus xanthus determined by pulsed-field gel electrophoresis," J. Bacteriol. 172(1990):4206-4213.
2523. Jean-Michel Claverie, "What if there are only 30,000 human genes?" Science 291(16 February 2001):1255-1257; see also http://www.airbus.com/.

2524. Michael W.W. Adams, "The influence of environment and metabolic capacity on the size of a microorganism," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel2adams.htm.

2525. Lothar Steidler, Sabine Neirynck, Nathalie Huyghebaert, Veerle Snoeck, An Vermeire, Bruno Goddeeris, Eric Cox, Jean Paul Remon, Erik Remaut, "Biological containment of genetically modified Lactococcus lactis for intestinal delivery of human interleukin 10," Nature Biotechnology (15 June 2003).

2526. P. Segers, M. Vancanneyt, B. Pot, U. Toruck, B. Hoste, D. Dewettinck, E. Falsen, K. Kersters, P. DeVos, "Classification of *Pseudomonas diminuta* Leifson and Hugh 1954 and *Pseudomonas vesicularis* Busing, Doll, and Freytag 1953 in *Brevundimonas* gen. nov. as *Brevundimonas diminuta* comb. nov. and *Brevundimonas vesicularis* comb. nov., respectively," Int. J. Syst. Bacteriol. 44(1994):499-510.

2527. D.K. Button, Betsy Robertson, "Properties of small free-living aquatic bacteria," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel2button.htm.

2528. J.J.Y. Joel, X. Cui, J. Reizer, M.H.J. Saier, "Regulation of the glucose: H$^+$ symporter by metabolite-activated ATP-dependent phosphorylation of HPr in *Lactobacillus brevis*," J. Bacteriol. 176(1994):3484-3492.

2529. Donald A. Bryant, ed., The Molecular Biology of Cyanobacteria, Kluwer Academic Publishers, New York, 1995; P. Fay, C. Van Baalen, eds., Cyanobacteria: A Comprehensive Review, Elsevier Science Ltd., 1987.

2530. David L. Herrin, "Lecture 8: Nuclear genome of plants," Bio350M/Bio388M, Plant Molecular Biology, University of Texas, Fall 2002; http://www.esb.utexas.edu/bot350m/lecnotes/Nucleargen1.ppt.

2531. Aristides Requicha, personal communication to Robert A. Freitas Jr., 29 September 2003.

2532. Gunter P. Wagner, "Adaptation and the Modular Design of Organisms," Center for Computational Ecology, Yale University, New Haven, CT, 1995; http://www.cbc.yale.edu/old/cce/papers/ALife/alife.html.

2533. E. Szathmary, L. Wolpert, "The evolution of multicellularity," in P. Hammerstein, ed., Genetic and Social Mechanisms of Cooperation, MIT Press, Cambridge, MA, 2003.

2534. A. Wilkins, The Evolution of Developmental Pathways, Sinauer Associates, Sunderland, MA, 2002.

2535. Chris Langton, personal communication to Robert A. Freitas Jr., 7 October 2003.

2536. C. Gans, R.G. Northcutt, "Neural crest and the origin of vertebrates: A new head," Science 220(1983):268-274.

2537. M.J. Zigmond, F.E. Bloom, S.C. Landis, J.L. Roberts, L.R. Squire, eds., Fundamental Neuroscience, Academic Press, London, 1999.

2538. E. Marin, G.S.X.E. Jeffries, T. Komiyama, H. Zhu, L. Luo, "Representation of the glomerular olfactory map in the Drosophila brain," Cell 109(2002):243-255.

2539. Dan G. Fraenkel, "Metabolism and physiology of conventional bacteria," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel1fraenkel.htm.

2540. Geoffrey B. West, James H. Brown, Brian J. Enquist, "A general model for the origin of allometric scaling laws in biology," Science 276(4 April 1997):122-126. See also: G.B. West et al, "The fourth dimension of life, fractal geometry, and allometric scaling of organisms," Science, 284(1999):1677-1679; G.B. West et al, "Allometric scaling of metabolic rate from molecules and mitochondria to cells and mammals," Proc. Natl. Acad. Sci. (USA) 99(2002):2473-2478.

2541. T. Fenchel, "Intrinsic rate increase: the relationship with body size," Oecologia 14(1974):317-326.

2542. Roger M. Knutson, Fearsome Fauna: A Field Guide to the Creatures Who Live in You, W.H. Freeman and Company, New York, 1999.

2543. "Section 2403: Deposit of Biological Material (37 CFR 1.801 Biological Material)" and "Section 2403.01: Material Capable of Self-Replication," Manual of Patent Examining Procedure, Rev. 3, 6th Edition, Office of Classification Support, U.S. Patent and Trademark Office; http://www.internet-patents.com/Manual%20PEP/411.htm.

2544. Zachary Mason, "Programming with stigmergy: using swarms for construction," in Russell K. Standish, Hussein A. Abbass, Mark A. Bedau, eds., Artificial Life VIII, 8th Intl. Conf. on the Simulation and Synthesis of Living Systems, University of New South Wales, Australia, 9-13 December 2002, MIT Press, Cambridge, MA, 2000, pp. 371-374; http://parallel.acsu.unsw.edu.au/complex/alife8/proceedings/sub2157.pdf.

2545. P. Gonczy, et al, "Functional genomic analysis of cell division in C. elegans using RNAi of genes on chromosome III," Nature 408(2000):331-336.

2546. J.C. King, "The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies," J. Nutr. 133(May 2003):1732S-1736S.

2547. H. Sohma, "Pregnancy and the teeth," Shigaku. 50(December 1962):199-201 (in Japanese); A. Prochonczukow, "Effect of pregnancy on the protein metabolism in the teeth and jaws," Czas. Stomatol. 19(May 1966):491-495 (in Polish); F. Frumento, "Behavior of some mineral-ion components of teeth during pregnancy," Riv. Ital. Stomatol. 21(July 1966):705-711 (in Italian); M. Orosz, K. Gabris, T. Zelles, "Longitudinal study of gums and teeth during pregnancy," Fogorv. Sz. 73(January 1980):18-21 (in Hungarian); Jason S. Kasarsky, "Dental Health During Pregnancy: Tooth Loss and Decay," January 2004; http://www.jkdds.com/html/dental_health_during_pregnancy.html.

2548. D. Fitzsimons, J.T. Dwyer, C. Palmer, L.D. Boyd, "Nutrition and oral health guidelines for pregnant women, infants and children," J. Am. Diet. Assoc. 98(February 1998):182-186, 189; J. Am. Diet. Assoc. 98(March 1998):264 (erratum). See also: C. Crawley, "A Tooth for Every Child?" FNH 8-9 Dental Health, FACS Extension, College of Family and Consumer Sciences, University of Georgia, March 1998, http://www.fcs.uga.edu/extension/internal/fcsnews/3-98/18.html; Alan Green, "Pregnancy and Natural Dentistry," 2002, http://kimberley.rivero.com/test/article_pregnancy.htm; Craig Segal, "The Truth About Old Wives' Tales: Teeth," Reader's Digest Canada, 2003, http://www.readersdigest.ca/mag/2001/12/wives.html; Crystal Dupay, "Pregnancy and Your Oral Health," 2003, http://www.mainstreetmom.com/preg_oral_health.htm; Allyson K. Hurley, "Watch Your Mouth: Part 1," 2004, http://www.allysonhurley.com/articles.html; Rajiv S. Khosla, "Pregnancy and Dentistry," Mumbai, India, 2004, http://www.geocities.com/drkhosla1/pregnancy.html.

2549. "In Depth: Calcium and Pregnancy. Your Unborn Child Will Draw the Calcium It Needs From Your Body," Consumer Healthcare Research & Development, GlaxoSmithKline, CALCIUMinfo.com, The Online Calcium Information Resource, 2004; http://www.calciuminfo.com/pages/2_3preg.htm. See also: Dan Peterson, "Dental Health Tips for Pregnancy," DentalNotes, Winter 2002; http://www.dentalgentlecare.com/new_page_17.htm. See also: Lt. Col. Henry Greene, "Dental Care Myths," Scott Fall Newsletter, Army News Service, 24 January 2000; and at: "Sub-Section 1.10. Dental Care, 1-333: Dental Care Myths," General Health Information, USAF Retiree Activities Office, 28 March 2002; http://public.scott.amc.af.mil/375aw/rao/Section1/SSec1.10.htm#1-333, http://www.geocities.com/alpost42/files/rao112.htm, http://www.post593.org/RAO/DENTAL%20CARE%20Myths.htm, and http://www.drhledin.com/dentalmyths.htm.

2550. W.M. Ringsdorf Jr., R.F. Flatland, K.G. Lindsey, E. Cheraskin, "Clinical tooth mobility and pregnancy," Obstet. Gynecol. 17(April 1961):434-438; K.H. Rateitschak, "Tooth mobility changes in pregnancy," J. Periodontal Res. 2(1967):199-206; E. Hellsing, L. Hammarstrom, "The effects of pregnancy and fluoride on orthodontic tooth movements in rats," Eur. J. Orthod. 13(June 1991):223-230.

2551. "Dental Caries. Contributing Factors in Dental Caries: Systemic Factors," Department of Oral Medicine and Pathology, The University of Alberta, 2004; http://www.dent.ualberta.ca/path/355/Systemic_Factors.html.

2552. Steven Parham, "Robotic self-appraisal and reproduction," Kybernetes 24(1995):34-43; http://www.starjammer.org/downloads/parham.pdf.

2553. H. Harris, The Birth of the Cell, Yale University Press, New Haven, CT, 1999.

2554. T.J. Mitchison, E.D. Salmon, "Mitosis: a history of division," Nature Cell Biol. 3(2001):E17-E22.

2555. Jonathan M. Scholey, Ingrid Brust-Mascher, Alex Mogilner, "Cell division," Nature 422(17 April 2003):746-752; http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v422/n6933/full/nature01599_fs.html.

2556. Eberhard Becker, Willms Buhse, Dirk Gunnewig, Niels Rump, eds., Digital Rights Management: Technological, Economic, and Legal and Political Aspects, Springer-Verlag, New York, 2004.

2557. R.C. Allsopp, E. Chang, M. Kashefi-Aazam, E.I. Rogaev, M.A. Piatyszek, J.W. Shay, C.B. Harley, "Telomere shortening is associated with cell division in vitro and in vivo," Exp. Cell Res. 220(September 1995):194-200; David Kipling, The Telomere, Oxford University Press, 1997; U. Friedrich, E. Griese, M. Schwab, P. Fritz, K. Thon, U. Klotz, "Telomere length in different tissues of elderly patients," Mech. Ageing Dev. 119(15 November 2000):89-99. See telomere image at http://www.ornl.gov/TechResources/Human_Genome/graphics/slides/ttelomeres.html.

2558. S.C. Stearns, "The influence of size and phylogeny on patterns of covariation among life-history traits in mammals," Oikos 41(1983):173-187.

2559. John Whitfield, "Westerners breed like 30-tonne gorillas," Nature ScienceUpdate, 10 April 2003; http://www.nature.com/nsu/030407/030407-9.html.

2560. Melanie E. Moses, James H. Brown, "Allometry of human fertility and energy use," Ecology Letters 6(2003):295-300.

2561. Derek Harter, Max Garzon, "Replication control mechanisms for autonomous computing," Department of Mathematical Sciences, University of Memphis, 21 September 1999; http://www.msci.memphis.edu/~harterd/RepControlProject/version0/repcontrol/repcontrol.html or http://www.msci.memphis.edu/~harterd/RepControlProject/version0/repcontrol.ps.

2562. R.P. Spencer, "Cessation of reproduction: an analytic view of menopause," Med. Hypotheses 59(October 2002):406-410; A. Vermeulen, "Environment, human reproduction, menopause, and andropause," Environ. Health Perspect. 101(July 1993):91-100; W.J. Francis, "Reproduction at menarche and menopause in women," J. Reprod. Fertil. Suppl. 12(March 1970):89-98.

2563. L. Wolff, S. Ruscetti, "Malignant transformation of erythroid cells in vivo by introduction of a nonreplicating retrovirus vector," Science 228(28 June 1985):1549-1552.

2564. H.E. Gruber, K.D. Finley, R.M. Hershberg, S.S. Katzman, P.K. Laikind, J.E. Seegmiller, T. Friedmann, J.K. Yee, D.J. Jolly, "Retroviral vector-mediated gene transfer into human hematopoietic progenitor cells," Science 230(29 November 1985):1057-1061.

2565. Ahmed H. Zewail, "Femtochemistry. Past, present, and future," Pure Appl. Chem. 72(December 2000):2219-2231; http://www.iupac.org/publications/pac/2000/7212/7212pdfs/7212zewail_2219.pdf. See also: Ahmed H. Zewail, "Femtochemistry: atomic-scale dynamics of the chemical bond using ultrafast lasers," Angew. Chem. Intl. Ed. 39(2000):2586-2631.

2566. Anatoly K. Khitrin, Vladimir L. Ermakov, Bing M. Fung, "Nuclear magnetic resonance molecular photography," J. Chem. Phys. 117(15 October 2002):6903-6906; http://ermakov.smtp.ru/pdf/ermakov_jcp117p6903.pdf or http://arxiv.org/pdf/quant-ph/0208136. See also: Will Knight, "Digital image stored in single molecule," NewScientist.com, 1 December 2002; http://www.newscientist.com/news/news.jsp?id=ns99993129, but note http://www.nano-tek.org/sci.nanotech/1547.html.

2567. Sergei Aleksandrovich Magnitskii, "Laboratory of Femtotechnology," http://msuilc.ilc.msu.su/labs/311/311.html; LMU Theoretical Femtoscience Group, http://www.cup.uni-muenchen.de/pc/devivie/index.html.

2568. Michael Conrad, "The geometry of evolutions," BioSystems 24(1990):61-81. See also: Michael Conrad, Adaptability, Plenum Press, New York, 1983.

2569. Lee Altenberg, "Chapter 3. The evolution of evolvability in genetic programming," in J.Kenneth E. Kinnear, ed., Advances in Genetic Programming, MIT Press, Cambridge, MA, 1994, pp. 47-74; http://dynamics.org/~altenber/PAPERS/EEGP/.

2570. John Stewart, "The evolution of genetic cognition," J. Soc. Evolutionary Syst. 20(1997):53-73; http://www4.tpg.com.au/users/jes999/gencog.htm.

2571. P. Hogeweg, "Multilevel evolution: Replicators and the evolution of diversity," Physica D 75(1994):275-291.

2572. J. Maynard Smith, "How to model evolution," in J. Dupre, ed., Essays on Evolution and Optimality, MIT Press, Cambridge, MA, 1987, pp. 119-131.

2573. P.M.B. Vitanyi, "Sexually reproducing cellular automata," Math. Biosci. 18(1973):23-54; P.M.B. Vitanyi, "Genetics of reproducing automata," Proc. 1974 Conf. on Biologically Motivated Automata Theory, IEEE, New York, 1974, pp. 166-171; P.M.B. Vitanyi, "On a problem in the collective behavior of automata," Discrete Mathematics 14(1976):99-101.

2574. Ralph Merkle, "The risks of nanotechnology," in B.C. Crandall, James Lewis, eds., Nanotechnology Research and Perspectives: Papers from the First Foresight Conference on Nanotechnology (October 1989), MIT Press, Cambridge, MA, 1992, pp. 287-294.

2575. J.H. Werren, J.D. Bartos, "Recombination in Wolbachia," Curr. Biol. 11(20 March 2001):431-435; R. Stouthamer, J.A. Breeuwer, G.D. Hurst, "Wolbachia pipientis: microbial manipulator of arthropod reproduction," Annu. Rev. Microbiol. 53(1999):71-102; S.P. Sinkins, H.R. Braig, S.L. O'Neill, "Wolbachia superinfections and the expression of cytoplasmic incompatibility," Proc. R. Soc. Lond. B. Biol. Sci. 261(22 September 1995):325-330; L.D. Hurst, "The evolution of cytoplasmic incompatibility or when spite can be successful," J. Theoret. Biol. 148(21 January 1991):269-277.

2576. J.H. Werren, D.M. Windsor, "Wolbachia infection frequencies in insects: Evidence of global equilibrium?" Proc. R. Soc. Lond. B. Biol. Sci. 267(7 July 2000):1277-1285; S.R. Bordenstein, F.P. O'Hara, J.H. Werren, "Wolbachia-induced incompatibility precedes other hybrid incompatibilities in Nasonia," Nature 409(8 February 2001):707-710, 675-677 (comment).

2577. David Blair, "Nature foils poachers as elephants shed tusks," Daily Telegraph, 24 September 1998; http://www.gaiabooks.co.uk/environment/elephants_tuskless.html.

2578. "Hummingbirds, Rattlesnakes and Crayfish," Casa Nuestra Winery & Vineyards, No. 29, November 2000; http://www.casanuestra.com/journal_29.htm.

2579. S. Mitsuhashi, "Drug resistance in bacteria: history, genetics and biochemistry," J. Int. Med. Res. 21(January-February 1993):1-14.

2580. A.A. Hoffmann, R.J. Hallas, J.A. Dean, M. Schiffer, "Low potential for climatic stress adaptation in a rainforest Drosophila species," Science 301(4 July 2003):100-102.

2581. Anders Sandberg, "Limiting the evolution of replicators," http://www.aleph.se/Trans/Tech/Complexity/replicator.html.

2582. Meng-Chao Yao, Patrick Fuller, Xiaohui Xi, "Programmed DNA deletion as an RNA-guided system of genome defense," Science 300(6 June 2003):1581-1584, 1517-1518 (comment).

2583. C.H. Waddington, "Canalization of development and the inheritance of acquired characters," Nature 150(1942):563.

2584. Elizabeth M. Boon, Alison L. Livingston, Nikolas H. Chmiel, Sheila S. David, Jacqueline K. Barton, "DNA-mediated charge transport for DNA repair," Proc. Natl. Acad. Sci. (USA) 100(28 October 2003):12543-125437; http://www.pnas.org/cgi/content/full/100/22/12543. See also: M.A. O'Neill, C. Dohno, J.K. Barton, "Direct chemical evidence for charge transfer between photoexcited 2-aminopurine and guanine in duplex DNA," J. Am. Chem. Soc. 126(11 February 2004):1316-1317.

2585. M. Eigen, W. Gardiner, P. Schuster, R. Winkler-Oswatitsch, "The origin of genetic information," Sci. Amer. 244(April 1981):78-94.

2586. Dongsu Bak, "Replication error and time evolution of a self-replicating system," Report No. UOSTP-99-005, 1999; http://arxiv.org/pdf/adap-org/9903005.

2587. Martin Nilsson, Nigel Snoad, "Error thresholds for quasi-species on dynamic fitness-landscapes," Santa Fe Institute, 24 September 1999; http://fy.chalmers.se/~martin/errorthresholds.ps.gz.

2588. Orazio Miglino, Richard Walker, "Genetic redundancy in evolving populations of simulated robots," Artificial Life 8(Summer 2002):265-278; http://mitpress.mit.edu/catalog/item/default.asp?sid=2AC0A07D-41B4-44CE-AB40-CAA5E0D78F32&ttype=6&tid=9232 (abstract).

2589. I. Birol, S.J. Parulekar, F. Teymour, "Effect of environment partitioning on the survival and coexistence of autocatalytic replicators," Phys. Rev. E Stat. Nonlin. Soft. Matter Phys. 66(November 2002):051916.

2590. S.F. Gilbert, ed., Developmental Biology, 6th edition, Sinauer Associates, Sunderland, MA, 2000, p. 554.

2591. R.P. Ellinson, "Change in developmental patterns: Embryos of amphibians with large eggs," in R.A. Raff, E.C. Raff, eds., Development as an Evolutionary Process, Alan R. Liss, New York, 1987, pp. 1-21.

2592. S.R. Voss, H.B. Shaffer, "Adaptive evolution via a major gene effect: Paedomorphosis in the Mexican axolotl," Proc. Natl. Acad. Sci. (USA) 94(1997):14185-14189.

2593. H. Hoenigsberg, "Cell biology, molecular embryology, Lamarckian and Darwinian selection as evolvability," Genet. Mol. Res. 2(31 March 2003):7-28.

2594. N.W. Blackstone, A.M. Ellison, "Maximal indirect development, set-aside cells, and levels of selection," J. Exp. Zool. 288(15 August 2000):99-104; Andrew Ransick, R. Andrew Cameron, Eric H. Davidson, "Postembryonic segregation of the germ line in sea urchins in relation to indirect development," Proc. Natl. Acad. Sci. (USA) 93(25 June 1996):6759-6763; http://www.pnas.org/cgi/reprint/93/13/6759.
2595. H.M. Temin, "Reverse transcriptases. Retrons in bacteria," Nature 339(25 May 1989):254-255.
2596. J.A. Marcum, "From heresy to dogma in accounts of opposition to Howard Temin's DNA provirus hypothesis," Hist. Philos. Life Sci. 24(2002):165-192.
2597. D. Baltimore, "Viral RNA-dependent DNA polymerase. 1970," Biotechnology 24(1992):3-5.
2598. S.P. Otto, I.M. Hastings, "Mutation and selection within the individual," Genetica 102-103(1998):507-524.
2599. R. Jain, M.C. Rivera, J.E. Moore, J.A. Lake, "Horizontal gene transfer in microbial genome evolution," Theor. Popul. Biol. 61(June 2002):489-495.
2600. Viroids: Section 4.3.2. Ribosomes: Section 4.2. Bacteria, Viruses, Bacteria, Protozoa, Birds, Trees: Philip L. Altman, Dorothy S. Dittmer, eds., Biology Data Book, Federation of American Societies for Experimental Biology, Washington DC, 1964, pp. 51-52, 82, 110; also see http://www.amazilia.net/MIHummerNet/DataColl.htm; http://www.rubythroat.org/RTHUReproductionMain.html; http://camfilfarr.ballou.se/pdf/bacteria_chart.pdf. Insects: M.H. Dickinson, J.R.B. Lighton, "Muscle efficiency and elastic storage in the flight motor of Drosophila," Science 268(7 April 1995):87-90; also see http://www.geocities.com/Yosemite/Trails/5335/Animals/honeybee.html; http://www.eap.mcgill.ca/Publications/EAP53.htm; http://www.museums.org.za/bio/spiderweb/reproduction.htm; http://www.ceolas.org/fly/intro.html. Reptile: http://www.lclark.edu/~autumn/dept/geckostory.html; http://www.gekkota.com/html/gekko_gecko.html. Mammals: Truett Allison, D. Cicchetti, "Sleep in mammals: ecological and constitutional correlates," Science 194(12 November 1976):732-734, http://lib.stat.cmu.edu/datasets/sleep; also see http://www.animalinfo.org.
2601. Jyrki E.I. Hokkanen, "The size of the largest land animal," J. Theor. Biol. 118(1986):491-499; http://www.helsinki.fi/~jyhokkan/largest.htm (abstract), http://www.miketaylor.org.uk/dino/hokkanen/Size-Hokkanen.html (paper), http://www.miketaylor.org.uk/dino/hokkanen/Size-Hokkanen.doc (paper).
2602. John Tyler Bonner, Size and Cycle: An Essay on the Structure of Biology, Princeton University Press, Princeton, NJ, 1965.
2603. G.B. West, J.H. Brown, B.J. Enquist, "A general model for ontogenetic growth," Nature 413(11 October 2001):628-631.
2604. Robert Henry Peters, The Ecological Implications of Body Size, Cambridge University Press, Cambridge, 1983.
2605. Eric L. Charnov, Life History Invariants: Some Explorations of Symmetry in Evolutionary Ecology, Oxford University Press, New York, 1993.
2606. R.M. May, "The dynamics and diversity of insect faunas," in L.A. Mound, N. Waloff, eds., Diversity of Insect Faunas, Blackwell Scientific, Oxford, 1978, pp. 188-204.
2607. R.M. May, "The search for patterns in the balance of nature — advances and retreats," Ecology 67(1986):1115-1126.
2608. John Tyler Bonner, The Evolution of Complexity by Means of Natural Selection, Princeton University Press, Princeton, NJ, 1988.
2609. T.A. McMahon, J.T. Bonner, On Size and Life, Scientific American Library, New York, 1983.
2610. J.H. Brown, Macroecology, University of Chicago Press, Chicago, 1995.
2611. Brian A. Maurer, "Adaptive diversification of body size: The roles of physical constraint, energetics, and natural selection," Michigan State University preprint, 2002; http://www.msu.edu/~maurerb/Adaptive diversification, 2.0.pdf.
2612. J.H. Brown, B.A. Maurer, "Evolution of species assemblages: effects of energetic constraints and species dynamics on the diversification of the North American avifauna," Amer. Naturalist 130(1987):1-17.
2613. J.H. Brown, P.A. Marquet, M.L. Taper, "Evolution of body-size — consequences of an energetic definition of fitness," Amer. Naturalist 142(1993):573-584.
2614. J. Kozlowski, "Energetic definition of fitness? Yes, but not that one," Amer. Naturalist 147(1996):1087-1091.
2615. S.L. Chown, K.J. Gaston, "The species-body size distribution: energy, fitness and optimality," Functional Ecology 11(1997):365-375.
2616. B.A. Maurer, "The evolution of body size in birds. II. the role of reproductive power," Evolutionary Ecology 12(1998):935-944.
2617. F. Bokma, "Evolution of body size: limitations of an energetic definition of fitness," Functional Ecology 15(2001):696-699.
2618. R.W. Sheldon, A. Prakash, W.H. Sutcliffe, Jr., "The size distribution of particles in the ocean," Limnol. Oceanogr. 17(1972):327-340.
2619. S.R. Kerr, "Theory of size distribution in ecological communities," J. Fish. Res. Board Can. 31(1974):1859-1862.
2620. W.G. Sprules, M. Munawar, "Plankton size spectra in relation to ecosystem productivity, size and perturbation," Can. J. Fish. Aquat. Sci. 43(1986):1789-1794.
2621. J. Rodriguez, M.M. Mullin, "Relation between biomass and body weight of plankton in a steady-state oceanic ecosystem," Limnol. Oceanogr. 31(1986):361-370.
2622. W.G. Sprules, S.B. Brandt , D.J. Stewart, M. Munawar, E.H. Jin, J. Love, "Biomass size spectrum of the Lake Michigan pelagic food web," Can. J. Fish. Aquat. Sci. 48(1991):105-115.
2623. U. Gaedke, "The size distribution of plankton biomass in a large lake and its seasonal variability," Limnol. Oceanogr. 37(1992):1202-1220.
2624. Juan Camacho1, Ricard V. Sol, "Scaling and Zipf's Law in ecological size spectra," Santa Fe Institute Working Papers, 1999; http://www.santafe.edu/sfi/publications/Working-Papers/99-12-076.pdf.
2625. Eric R. Pianka, "On r and K selection," Amer. Naturalist 104(June 1970):592-597; reprinted in T.H. Clutton-Brock, P.H. Harvey, eds., Readings in Sociobiology, W.H. Freeman, San Francisco, 1978; http://uts.cc.utexas.edu/~varanus/rK.pdf.
2626. J.A. McNeely et al, Conserving the World's Biological Diversity, International Union for Conservation of Nature and Natural Resources, Gland, Switzerland; Wildlife Research Institute, World Wildlife Fund, Conservation International, and the World Bank, Washington, DC, 1990.
2627. Sankar Chatterjee, The Rise of Birds: 225 Million Years of Evolution, Johns Hopkins University Press, Baltimore, MD, 1997; http://www.press.jhu.edu/press/books/titles/sampler/chatjee.htm.
2628. T.L. Erwin, "Tropical forest canopies: the last biotic frontier," Bull. Entomological Soc. Amer. 29(1983):14-19.
2629. C.B. Williams, Patterns in the Balance of Nature and Related Problems in Quantitative Ecology, Academic Press, London, 1964.
2630. C.W. Sabrosky, "How many insects are there?" in Insects: The Yearbook of Agriculture, U.S. Department of Agriculture, Washington, DC, 1952.
2631. "Numbers of Insects (Species and Individuals)," Department of Entomology, National Museum of Natural History; http://www.si.edu/resource/faq/nmnh/buginfo/bugnos.htm.
2632. N.J. Palleroni, "Some reflections on bacterial diversity," Amer. Soc. Microbiol. News 60(1994):537-540.
2633. V. Torsvik, J. Goksoyr, F.L. Daae, "High diversity in DNA of soil bacteria," Appl. Envir. Microbiol. 56(1990):782-787; E.O. Wilson, The Diversity of Life, Belknap Press, Cambridge, MA, 1992.
2634. H. Sugawara, J. Ma, S. Miyazaki, J. Shimura, Y. Takashima, World Directory of Collections of Cultures of Microorganisms, Fourth edition, World Federation of Culture Collections Data Center on Microorganisms, Saitama, Japan, 1993; http://www.wdcm.riken.go.jp.
2635. Roche Facets, "Antibiotic resistance gives cause for concern"; http://www.roche.com/pages/facets/5/atnibiotic.htm.
2636. D.L. Hawksworth, "The fungal dimension of biodiversity: Magnitude, significance and conservation," Mycol. Res. 95(1991):641-655.
2637. R.M. May, "How many species are there on earth?" Science 241(16 September 1988):441-1449.
2638. Thomas P. Curtis, William T. Sloan, Jack W. Scannell, "Estimating prokaryotic diversity and its limits," Proc. Natl. Acad. Sci. (USA) 99(6 August 2002):10494-10499; http://www.pnas.org/cgi/content/full/99/16/10494; B.B. Ward, "How many species of prokaryotes are there?" Proc. Natl. Acad. Sci. (USA) 99(6 August 2002):10234-10236.
2639. William B. Whitman, David C. Coleman, William J. Wiebe, "Prokaryotes: The unseen majority," Proc. Natl. Acad. Sci. (USA) 95(9 June 1998):6578-6583; http://www.pnas.org/cgi/content/abstract/95/12/6578.
2640. R. Himmelreich, H. Hilbert, H. Plagens, E. Pirkl, B.C. Li, R. Herrmann, "Complete sequence analysis of the genome of the bacterium Mycoplasma pneumoniae," Nucleic Acids Res. 24(1996):4420-4449.

2641. Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanomenu.htm.

2642. Gretchen Vogel, "Finding life's limits," Science 282(20 November 1998):1399.

2643. D.S. McKay, E.K. Gibson Jr., K.L. Thomas-Keprta, H. Vali, C.S. Romanek, S.J. Clemett, X.D.F. Chillier, C.R. Maechling, R.N. Zare, "Search for past life on Mars: Possible relic biogenic activity in Martian meteorite ALH84001," Science 273(16 August 1996):924-930; A.H. Treiman, "The history of Allan Hills 84001 revised: Multiple shock events," Meteoritics & Planetary Science 33(1998):753-764.

2644. V.A. Pedone, R.L. Folk, "Formation of aragonite cement by nannobacteria in the Great Salt Lake, Utah," Geology 24(1996):763-765; R.L. Folk, F.L. Lynch, F.L., "Nannobacteria are alive on Earth as well as Mars," in R.B. Hoover, ed., Proc. SPIE, 3111(1997):406-419; R.L. Folk, F.L. Lynch, "The possible role of nannobacterial (dwarf bacteria) in clay-mineral diagenesis and the importance of careful sample preparation in high-magnification SEM study," J. Sedimentary Res. 67(1997):583-589; R.L. Folk, "Nannobacteria and the precipitation of carbonates in unusual environments," Sedimentary Geology 126(1999):47-56; R.L. Folk, F.L. Lynch, "Organic matter, putative nannobacteria, and the formation of Ooids and Hardgrounds," Sedimentology 48(2001):215-229.

2645. A. Iida, J. Akai, "TEM study on magnetotactic bacteria and contained magnetite grains as biogenic minerals, mainly from Hokuriku-Niigata region, Japan," Sci. Rep. Niigata Univ., Ser E (Geology) 11(1996):43-66.

2646. M. Posfai, P.R. Buseck, D.A. Bazylinski, R.B. Frankel, "Reaction sequence of iron sulfide minerals in bacteria and their use as biomarkers," Science 280(8 May 1998):880-883.

2647. R. Symonds, "Scanning electron microscope observations of sublimates from Merapi Volcano, Indonesia," Geochem. J. 26(1993):337-350; J.P. Bradley, R.P. Harvey, H.Y. McSween Jr., "Non-biologic origin of 'nannofossils' in Martian meteorite ALH84001," Nature 390(1997):454-455.

2648. M.T. MacDonnell, M.A. Hood, Appl. Environ. Microbiol. 43(1982):566-571.

2649. S. Kjelleberg, M. Hermansson, P. Marden, G.W. Jones, "The transient phase between growth and nongrowth of heterotrophic bacteria, with emphasis on the marine environment," Annu. Rev. Microbiol. 41(1987):25-49.

2650. D.B. Roszak, R.R. Colwell, "Survival strategies of bacteria in the natural environment," Microbiol. Rev. 51(1987):365-379.

2651. M. Eguchi, T. Nishikawa, K. Macdonald, R. Cavicchioli, J.C. Gottschal, S. Kjelleberg, "Responses to stress and nutrient availability by the marine ultramicrobacterium *Sphingomonas* sp. strain RB2256," Appl. Environ. Microbiol. 62(1996):1287-1294.

2652. F. Schut, J.C. Gottschal, R.A. Prins, "Isolation and characterization of the marine ultramicrobacterium Sphingomonas sp. strain RB2256," FEMS Microbiol. Rev. 20(1997):363-369.

2653. E.O. Kajander, I. Kuronen, K. Akerman, A. Pelttaari, N. Ciftcioglu, "Nanobacteria from blood, the smallest culturable autonomously replicating agent on Earth," SPIE 3111(1997):420-428.

2654. N. Ciftcioglu, A. Pelttari, E.O. Kajander, "Extraordinary growth phases of nanobacteria isolated from mammalian blood," Proc. SPIE 3111(1997):429-435.

2655. E. Olavi Kajander, Neva Ciftcioglu, "Nanobacteria: An alternative mechanism for pathogenic intra- and extracellular calcification and stone formation," Proc. Natl. Acad. Sci. (USA) 95(7 July 1998):8274-8279. See also: John Travis, "Nanobacteria strike the kidney again," Science News 155(19 June 1999):395, and http://www.nanobaclabs.com/.

2656. N. Ciftcioglu, M. Bjorklund, E.O. Kajander, "Stone formation and calcification by nanobacteria in human body," Proc. SPIE 3441(1998):105-111.

2657. E.O. Kajander, M. Bjorklund, N. Ciftcioglu, "Mineralization by nanobacteria," Proc. SPIE 3441(1998):86-94.

2658. Philippa J.R. Uwins, Richard I. Webb, Anthony P. Taylor, "Novel nano-organisms from Australian sandstones," Amer. Mineralogist 83(November/December 1998):1541-1550. See also: http://www.uq.edu.au/nanoworld/uwins.html and "Nanobiology" at http://naturalscience.com/ns/links/nanobiol.html.

2659. M. Bjorklund, N. Ciftcioglu, E.O. Kajander, "Extraordinary survival of nanobacteria under extreme conditions," Proc. SPIE 3441(1998):123-129.

2660. N. Ciftcioglu, E.O. Kajander, "Interaction of nanobacteria with cultured mammalian cells," Pathophysiology 4(1998):259-270.

2661. R.L. Folk, "SEM imaging of bacteria and nannobacteria in carbonate sediments and rocks," J. Sediment. Petrol. 63(1993):990-999; Robert Folk, Science 276(20 June 1997):1777.

2662. Harold J. Morowitz, "Biological self-replicating systems," in F. M. Snell, ed., Progress in Theoretical Biology, Academic Press, New York, 1967, pp. 35-58.

2663. Peter B. Moore, "A biophysical chemist's thoughts on cell size," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel1moore.htm.

2664. Steven A. Benner, "How small can a microorganism be?" in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel4benner.htm.

2665. A. Rich, "On the problems of evolution, and biochemical information transfer," in M. Kasha, B. Pullman, eds., Horizons in Biochemistry, Academic Press, New York, 1962, pp. 103-126.

2666. C.R. Woese, The Genetic Code. The Molecular Basis for Genetic Expression, Harper & Row, New York, 1967.

2667. L.E. Orgel, "Evolution of the genetic apparatus," J. Mol. Biol. 38(1968):381-393.

2668. F.H.C. Crick, "The origin of the genetic code," J. Mol. Biol. 38(1968):367-379.

2669. W. Gilbert, "The RNA world," Nature 319(1968):618.

2670. G.F. Joyce, A.W. Schwartz, S.L. Miller, L.E. Orgel, L.E., "The case for an ancestral genetic system involving simple analogs of the nucleotides," Proc. Natl. Acad. Sci. (USA) 84(1987):4398-4402.

2671. G.F. Joyce, "Foreword," in D.W. Deamer, G.R. Fleischaker, eds., Origins of Life: The Central Concepts, Jones and Bartlett, Boston, 1994.

2672. James P. Ferris, "Primitive life: origin, size, and signature," in Space Studies Board, Size Limits of Very Small Microorganisms: Proceedings of a Workshop, National Research Council, National Academy Press, Washington DC, 1999; http://www.nationalacademies.org/ssb/nanopanel4ferris.htm.

2673. F. Schut, R.A. Prins, J.C. Gottschal, "Oligotrophy and pelagic marine bacteria: facts and fiction," Aquat. Microb. Ecol. 12(10 April 1997):177-202.

2674. P.H. Janssen, A. Schuhmann, E. Morschel, F.A. Rainey, "Novel anaerobic ultramicrobacteria belonging to the Verrucomicrobiales lineage of bacterial descent isolated by dilution culture from anoxic rice paddy soil," Appl. Environ. Microbiol. 63(1997):1382-1388.

2675. Carl Woese, "The universal ancestor," Proc. Nat. Acad. Sci. (USA) 95(1998):6854-6859; http://www.pnas.org/cgi/content/full/95/12/6854.

2676. Richard Cowen, "What was the earliest living organism?" Department of Geology, University of California at Davis, 23 August 2001; http://www-geology.ucdavis.edu/~GEL3/firstlife.html.

2677. "How Old is the Universe?" Wilkinson Microwave Anisotropy Probe (WMAP) mission, NASA/Goddard Space Flight Center, 13 January 2004; http://map.gsfc.nasa.gov/m_uni/uni_101age.html.

2678. Christopher S. Kochanek, "The Mass of the Milky Way galaxy," Astrophys. J. 457(January 1996):228; http://cdsads.u-strasbg.fr/cgi-bin/bib_query?1996ApJ…457.228K.

2679. Robert Freitas, Tom McKendree, Anthony G. Francis; Jr., Tihamer Toth-Fejel, "Self-replication and nanotechnology," The Assembler 4(Fourth Quarter 1996):4-10; http://www.islandone.org/MMSG/9612.html#TofC4.

2680. J.B.S. Haldane, "The origin of life," New Biology 16(1954):12.

2681. D. Deutsch, The Fabric of Reality, Penguin Press, New York, 1997, p. 179.

2682. D.R. Mills, R.L. Peterson, S. Spiegelman, "An extracellular Darwinian experiment with a self-duplicating nucleic acid molecule," Proc. Natl. Acad. Sci. (USA) 58(July 1967):217-224.

2683. P.O. Luksha, A.D. Plekhanov, "New approach to the concept of information," ISSS'03 Conference Proceedings, Crete, Greece, 2003; http://www.geocities.com/CapeCanaveral/Hangar/8933/papers/New_appr_info.pdf.

2684. "Looking Back: River Rouge," Forbes 161(18 May 1998):122, 124, 128.

2685. Robert A. Freitas Jr., "The future of nanofabrication and molecular scale devices in nanomedicine," Studies in Health Technol. Inform. 80(2002):45-59; http://www.rfreitas.com/Nano/FutureNanofabNMed.htm.

2686. W. Fontana, L.W. Buss, "The arrival of the fittest: toward a theory of biological organization," Bull. Math. Biol. 56(1994):1-64.

2687. Lee C.F. Sallows, "In quest of a pangram," Abacus 2(Spring 1985):22-40; Lee C.F. Sallows, "Reflexicons," Word Ways 25(August 1992):131-141 (see also February 1992 and May 1992 issues); Eric Wassenaar, "Self-enumerating pangrams: A logological history," 17 April 1999, http://www.fatrazie.com/EWpangram.html; Tomoyuki Tanaka, "Self-doc pangrams or 'Sallowsgrams'," http://www.cs.indiana.edu/~tanaka/GEB/pangram.txt; "Solution to the /language/english/self.ref/self.ref.letters problem," http://rec-puzzles.org/sol.pl/language/english/self.ref/self.ref.letters.

2688. Edward Bock, Lunar Resources Utilization for Space Construction, General Dynamics Convair Division, GDC-ASP79001, Contract NAS9-15560, 1979. Also: Edward Bock, "Space-Based Manufacturing from Lunar-Derived Materials," Convair/General Dynamics Contractor Report, 1979.

2689. Rene H. Miller, David B.S. Smith, Extraterrestrial Processing and Manufacturing of Large Space Systems. Volumes 1-3, NASA Contract. No. NASA-32925, NASA CR-161293, Final Report, September 1979.

2690. Gerard K. O'Neill, Gerald Driggers, Brian O'Leary, "New routes to manufacturing in space," Astronautics and Aeronautics 18(October 1980):46-51; available for purchase from SSI at http://www.ssi.org/body_catalog.html.

2691. Elwood S. McCluskey, "Which vertebrates make Vitamin C?" Origins 12(1985):96-100; http://www.grisda.org/origins/12096.htm.

2692. Jeffrey D. Russell, Charles R. Kime, "System fault diagnosis: closure and diagnosability with repair," IEEE Trans. on Computers C-24(November 1975):1078-1089; Jeffrey D. Russell, Charles R. Kime, "System fault diagnosis: masking, exposure, and diagnosability without repair," IEEE Trans. on Computers C-24(December 1975):1155-1161.

2693. Peter J. Denning, "Fault tolerant operating systems," ACM Computing Surveys 8(1976):359-389.

2694. "Software Fault Tolerance: A Tutorial," NASA/Langley Research Center, Virginia, October 2000, NASA TM-2000-210616; http://www.hcs.ufl.edu/~cho/fault-tolerance/ft-NASA-2000.pdf.

2695. Shankar Vaidyanathan, Shivakumar Raman, "A framework for knowledge representation and interpretation of industrial objects," J. Manufacturing Systems 11(1992):93-101.

2696. H.H. Asada, "Manufacturing robotics: basic issues and challenges," in J.J. Gertler, J.B. Cruz Jr., M. Peshkin, L. Basanez, F. Nicolo, A. Ollero, eds., Proc. 13th World Congress, Intl. Federation of Automatic Control, Vol. A: Robotics, Components and Instruments, Pergamon Press, Oxford, UK, 1997, pp. 319-330.

2697. Lois Ericson, Anne Charles, Lennart Ericson, Opening and Closing Closures: Closures, Design and Sew, Watsonville, CA, 1996; http://www.designandsew.com/books.html#opening.

2698. Joseph Walsh, Endings in Clinical Practice: Effective Closure in Diverse Settings, Lyceum Books, Chicago, IL, 2003.

2699. John N. Gardner, Gretchen Van der Veer, The Senior Year: Facilitating Integration, Reflection, Closure, and Transition, Jossey-Bass, New York, 1997.

2700. Z. Fang, J.S. Deogun, "Closure properties of certain classes of languages under generalized morphic replication," Computer Journal 31(August 1988):325-329.

2701. D.A. Miller, Narrative and Its Discontents: Problems of Closure in the Traditional Novel, reprint edition, Princeton University Press, Princeton, NJ, 1989.

2702. R.G. Shelton, Closure, WLA Publishing, Phoenix, AZ, 2002.

2703. Alexander T. Trott, Wounds and Lacerations: Emergency Care and Closure, Second Edition, Mosby Publishing, St. Louis, MO, 1997.

2704. "Welcome to SIMD," SIMD Tech, 2003; http://www.simdtech.org/home.

2705. J. Parkinson, R. Gordon, "Beyond micromachining: the potential of diatoms," Trends in Biotechnol. 17(1999):190-196.

2706. K.H. Sandhage, M.B. Dickerson, P.M. Huseman, M.A. Caranna, J.D. Clifton, T.A. Bull, T.J. Heibel, W.R. Overton, M.E.A. Schoenwaelder, "Novel, bioclastic route to self-assembled, 3-D, chemically tailored meso-nanostructures: Shape-preserving reactive conversion of biosilica (diatom) microshells," Advanced Mater. 14(2002):429-433.

2707. A. Carbone, N.C. Seeman, "A route to fractal DNA-assembly," Natural Computing 1(2002):469-480; http://www.ihes.fr/PREPRINTS/M02/Resu/resu-M02-24.html (abstract), http://www.ihes.fr/PREPRINTS/M02/M02-24.pdf (paper).

2708. Pierre-Paul Grasse, "La reconstruction du nid et les coordinations inter-individuelles chez Bellicoitermes natalenis et Cubitermes sp. La theorie de la stigmergie: Essai d'interpretation des termites constructeurs," Insect Societies 6(1959):41-83.

2709. Guy Theraulaz, Eric Bonabeau, J.L. Deneubourg, "The algorithmic beauty of stigmergic patterns in social insects," Math. Sci. 435(1999):52-65; E. Bonabeau, S. Guerin, D. Snyers, P. Kuntz, G. Theraulaz, "Three-dimensional architectures grown by simple 'stigmergic' agents," BioSystems 56(2000):13-32; M. Dorigo, E. Bonabeau, G. Theraulaz, "Ant algorithms and stigmergy," Future Generation Computer Systems 16(2000):851-871.

2710. Guy Theraulaz, Eric Bonabeau, "Coordination in distributed building," Science 269(4 August 1995):686-688; Guy Theraulaz, Eric Bonabeau, "Modeling the collective building of complex architectures in social insects with lattice swarms," J. Theor. Biol. 177(1995):381-400; Guy Theraulaz, Eric Bonabeau, J.L. Deneubourg, "The origin of nest complexity in social insects," Complexity 3(1998):15-25; Guy Theraulaz, Eric Bonabeau, J.L. Deneubourg, N. Franks, O. Rafelsberger, J.L. Joly, S. Blanco, "A model for the emergence of pillars, walls and royal chamber in termite nests," Phil. Trans. R. Soc. London Ser. B Biol. Sci. 353(1998):1561-1576.

2711. Amorphous Computing HomePage; http://www.swiss.ai.mit.edu/projects/amorphous/.

2712. Radhika Nagpal, Gerry Sussman, "Robust Engineering Using Biologically-inspired Models of Cell Differentiation and Morphogenesis," MIT Artificial Intelligence Lab, 2003; http://www.swiss.ai.mit.edu/projects/amorphous/Robust/.

2713. W.W. Gropp, E.L. Lusk, "A taxonomy of programming models for symmetric multiprocessors and SMP clusters," Programming Models for Massively Parallel Computers (PMMP '95), 9-12 October 1995, Berlin, Germany, 1995; http://www-unix.mcs.anl.gov/~gropp/bib/papers/1995/taxonomy.pdf.

2714. David E. Culler, Jaswinder Pal Singh, Anoop Gupta, Parallel Computer Architecture: A Hardware/Software Approach, Morgan-Haufmann Publishers, 1999.

2715. William E. Johnston, "Rationale and strategy for a 21st century scientific computing architecture: The case for using commercial symmetric multiprocessors as supercomputers," Information and Computing Sciences Division, Lawrence Berkeley National Laboratory, LBNL Report No. 37661; http://www-itg.lbl.gov/~johnston/Scientific.Comp.Arch/Scientific.Comp.Arch.fm.html.

2716. "Cluster of SMPs," High Performance Computing Laboratory, University of New Mexico, 2003; http://hpc.eece.unm.edu/cluster.html.

2717. J.L. Potter, The Massively Parallel Processor, MIT Press, Cambridge, MA, 1985.

2718. Thomas E. Anderson, David E. Culler, David A. Patterson, NOW Team, "A case for NOW (Networks of Workstations)," IEEE Micro. 15(February 1995):54-64; http://www.cs.cornell.edu/Courses/cs614/2003SP/papers/ACP94.pdf.

2719. "Kelp Forest Exhibit: Kelp Cam," Monterey Bay Aquarium, 2003; http://www.mbayaq.org/efc/efc_hp/hp_kelp_cam.asp.

2720. Aristides A.G. Requicha, "Massively parallel nanorobotics for lithography and data storage," Intl. J. Robotics Res. 18(March 1999):344-350; http://www-lmr.usc.edu/~lmr/publications/ijrr98/.

2721. K.E. Drexler, "Molecular tip arrays for molecular imaging and nanofabrication," J. Vac. Sci. Technol. B 9(1991):1394-1397.

2722. Thomas R. Albrecht, Shinya Akamine, Mark J. Zdeblick, Calvin F. Quate, "Microfabrication of integrated scanning tunneling microscope," J. Vac. Sci. Technol. A 8(January/February 1990):317-318.

2723. M.I. Lutwyche, Y. Wada, "Observation of a vacuum tunnel gap in a transmission electron microscope using a micromechanical tunneling microscope," Appl. Phys. Lett. 66(22 May 1995):2807-2809.

2724. D.A. Walters, J.P. Cleveland, N.H. Thomson, P.K. Hansma, M.A. Wendman, G. Gurley, V. Elings, "Short cantilevers for atomic force microscopy," Rev. Sci. Instrum. 67(October 1996):3583-3590.

2725. D. Lange, M. Zimmermann, C. Hagleitner, O. Brand, H. Baltes, "CMOS 10-cantilever array for constant-force parallel scanning AFM," Technical Digest, Transducers '01, Vol. 2, 2001, pp. 1074-1077.

2726. T. Itoh, T. Suga, "Development of a force sensor for atomic force microscopy using piezoelectric thin films," Nanotechnology 4(1993):218-224. See also: T. Itoh, T. Suga, "Scanning force microscope using a piezoelectric microcantilever," J. Vac. Sci. Technol. B 12(1994):1581-1585; T. Itoh, T. Ohashi, T. Suga, "Scanning force microscope using piezoelectric excitation and detection," IEICE Trans. Electron. E78-C(1995):146-151; Toshihiro Itoh et al, "Independent parallel scanning force microscopy using Pb(Zr, Ti)O3 microcantilever array," Proc. MEMS'97, Nagoya, Japan, 1997.

2727. M. Tortonese, H. Yamada, R.C. Barrett, C.F. Quate, "Atomic force microscopy using a piezoresistive cantilever," Digest of Technical Papers, Sixth Intl. Conf. Solid-State Sensors and Actuators (Transducers '91), San Francisco, CA, 24-28 June 1991, pp. 448-451. See also: M. Tortonese, R.C. Barrett, C.F. Quate, "Atomic resolution with an atomic force microscope using piezoresistive detection," Appl. Phys. Lett. 62(22 February 1993):834-836.

2728. N. Blanc, J. Brugger, N.F. de Rooji, U. Durig, "Scanning force microscopy in the dynamic mode using microfabricated capacitive sensors," paper presented at the 8th Intl. Conf. Scanning Tunneling Microscopy/Spectroscopy and Related Techniques, STM '95, Snowmass Village, CO, 23-28 July 1995. See also: J. Brugger, R.A. Buser, N.F. de Rooij, "Micromachined atomic force microprobe with integrated capacitive readout," J. Micromech. Microeng. 2(1992):218-220.

2729. Fumiya Watanabe, Makoto Arita, H. Murayama, Teruaki Motooka, Ken Okano, Takatoshi Yamada, "Diamond tip arrays for parallel processing of microelectromechanical systems," Japan J. Appl. Phys. 37(1998):L562-L564.

2730. S.-J. Park, J. Chen, C. Liu, J.G. Eden, "Silicon microdischarge devices having inverted pyramidal cathodes: Fabrication and performance of arrays", Appl. Phys. Lett. 78(22 January 2001):419-421; http://mass.micro.uiuc.edu/publications/papers/50.pdf.

2731. Toshihiro Itoh, Takahiro Ohashi, Tadatomo Suga, "Piezoelectric cantilever array for multiprobe scanning force microscopy," MEMS-9, 1996, pp. 451-455.

2732. S.C. Minne, Ph. Flueckiger, H.T. Soh, C.F. Quate, "Atomic force microscope lithography using amorphous silicon as a resist and advances in parallel operation," J. Vac. Sci. Technol. B 13(May/June 1995):1380-1385.

2733. S.C. Minne, S.R. Manalis, C.F. Quate, "Parallel atomic force microscopy using cantilevers with integrated piezoresistive sensors and integrated piezoelectric actuators," Appl. Phys. Lett. 67(1995):3918-3920.

2734. S.R. Manalis, S.C. Minne, C.F. Quate, "Atomic force microscopy for high speed imaging using cantilevers with an integrated actuator and sensor," Appl. Phys. Lett. 68(1996):871-873.

2735. S.R. Manalis, S.C. Minne, A. Atalar, C.F. Quate, "Interdigital cantilevers for atomic force microscopy," Appl. Phys. Lett. 69(1996):3944-3946.

2736. K. Wilder, H.T. Soh, S.C. Minne, S.R. Manalis, C.F. Quate, "Cantilever arrays for lithography," Naval Research Reviews 49(1997):35-48.

2737. C.F. Quate, "Scanning probes as a lithography tool for nanostructures," Surf. Sci. 386(1997):259-264.

2738. S.C. Minne, S.R. Manalis, A. Atalar, C.F. Quate, "Independent parallel lithography using the atomic force microscope," J. Vac. Sci. Technol. B 14(1997):2456-2461.

2739. S.C. Minne, G. Yaralioglu, S.R. Manalis, J.D. Adams, J. Zesch, A. Atalar, C.F. Quate, "Automated parallel high speed atomic force microscopy," Appl. Phys. Lett. 72(4 May 1998):2340-2342; http://www.nano.unr.edu/adams/papers/auto_par.pdf.

2740. Kathryn Wilder, Calvin F. Quate, Bhanwar Singh, David F. Kyser, "Electron beam and scanning probe lithography: A comparison," J. Vac. Sci. Technol. B 16(November/December 1998):3864-3873.

2741. K. Wilder, D. Adderton, R. Bernstein, V. Elings, C.F. Quate, "Noncontact nanolithography using the atomic force microscope," Appl. Phys. Lett. 73(1998):2527-2529.

2742. S.C. Minne, J.D. Adams, G. Yaralioglu, S.R. Manalis, A. Atalar, C.F. Quate, "Centimeter scale atomic force microscope imaging and lithography," Appl. Phys. Lett. 73(21 September 1998):1742-1744; http://www.nano.unr.edu/adams/papers/cmscale.pdf.

2743. K. Wilder K, H.T. Soh, A. Atalar, C.F. Quate, "Nanometer-scale patterning and individual current-controlled lithography using multiple scanning probes", Rev. Sci. Instr. 70(1999):2822-2827.

2744. E.M. Chow, H.T. Soh, H.C. Lee, J.D. Adams, S.C. Minne, G. Yaralioglu, A. Atalar, C.F. Quate, T.W. Kenny, "Integration of through-wafer interconnects with a two-dimensional cantilever array", Sensors and Actuators A 83(2000):118-123.

2745. T. Sulchek, R.J. Grow, G.G. Yaralioglu, S.C. Minne, C.F. Quate, S.R. Manalis, A. Kiraz, A. Aydiner, A. Atalar, "Parallel atomic force microscopy with optical interferometric detection", Appl. Phys. Lett. 78(2001):1787-1789.

2746. J. Jason Yao, Susanne C. Arney, Noel C. MacDonald, "Fabrication of high frequency two-dimensional nanoactuators for scanned probe devices," J. Microelectromech. Syst. 1(March 1992):14-22.

2747. Z. Lisa Zhang, Noel C. MacDonald, "A RIE process for submicron, silicon electromechanical structures," J. Micromech. Microeng. 2(March 1992):31-38.

2748. Z. Lisa Zhang, N.C. MacDonald, "Integrated silicon process for micro-dynamic vacuum field emission cathodes," J. Vac. Sci. Technol. B 11(November/December 1993):2538-2543.

2749. Y. Xu, N.C. MacDonald, S.A. Miller, "Integrated micro-scanning tunneling microscope," Appl. Phys. Lett. 67(16 October 1995):2305-2307.

2750. Kaigham J. Gabriel, "Engineering microscopic machines," Sci. Amer. 273(September 1995):150-153.

2751. S. Arney, N.C. MacDonald, "Formation of submicron silicon on insulator structures by lateral oxidation of substrate-silicon islands," J. Vac. Sci. Technol. B 6(January/February 1988):341-345.

2752. J.P. Spallas, N.C. MacDonald, "Self-aligned silicon field emission cathode arrays formed by selective, lateral thermal oxidation of silicon," J. Vac. Sci. Technol. B 11(March/April 1993):437-440.

2753. Scott A. Miller, Kimberly L. Turner, Noel C. MacDonald, "Microelectromechanical scanning probe instruments for array architectures," Rev. Sci. Instrum. 68(November 1997):4155-4162. See also: http://www.news.cornell.edu/releases/March98/nanoprobe.bs.html.

2754. Robert F. Service, "Scanning scopes go parallel," Science 274(1 November 1996):723.

2755. "1000 Tips for Ultrahigh-Density Data Storage," IBM News, Zurich Research Lab, 11 October 1999, http://www.zurich.ibm.com/news/99/millipede.html; IBM Research: Millipede, http://domino.research.ibm.com/Comm/bios.nsf/pages/millipede.html.

2756. P. Vettiger, G. Cross, M. Despont, U. Drechsler, U. Duerig, B. Gotsmann, W. Haeberle, M. Lantz, H. Rothuizen, R. Stutz, G. Binnig, "The Millipede — nanotechnology entering data storage," Technical Report, IBM Zurich Research Lab; http://domino.research.ibm.com/Comm/bios.nsf/pages/millipede.html/$FILE/pv7201-preprint.pdf; also published in: IEEE Transactions on Nanotechnology (June 2002).

2757. "IBM's 'Millipede' Project Demonstrates Remarkable Trillion-Bit Data Storage Density," IBM Press Release, 11 June 2002; http://www-916.ibm.com/press/prnews.nsf/jan/F37FD677741C778A85256BD5004871CF.

2758. M.I. Lutwyche, M. Despont, U. Drechsler, U. Durig, W. Haberle, H. Rothuizen, R. Stutz, R. Widmer, G.K. Binnig, P. Vettiger, "Highly parallel data storage system based on scanning probe arrays," Appl. Phys. Lett. 77(13 November 2000):3299-3301.

2759. K.F. Bohringer, B.R. Donald, N.C. MacDonald, "Single-crystal silicon actuator arrays for micro manipulation tasks," Proc. IEEE 9th Intl. Workshop on Micro Electro Mechanical Systems (MEMS'96), San Diego CA, 11-15 February 1996, pp. 7-12; http://www.cs.cornell.edu/home/karl/MicroActuators.

2760. Dan Reznik, Stan Brown, John Camy, "Dynamic simulation as a design tool for a microactuator array," Proc. 1997 IEEE International Conference on Robotics and Automation, 20-25 April 1997, IEEE Robotics and Automation Society, pp. 1675-1680; http://www.cs.berkeley.edu/~jfc/dreznik/Pubs/icra97.pdf.

2761. N. Takeshima, H. Fujita, "Polyimide bimorph actuators for a ciliary motion system," ASME WAM, Symp. Micromech. Sensors, Actuators, and Systems, 1991.

2762. M. Ataka, A. Omodaka, H. Fujita, "A biometric micro system — a ciliary motion system," Tech. Digest, 7th Intl. Conf. Solid-State Sensors and Actuators (Transducers'93), Yokohama, Japan, 7-10 June 1993, pp. 38-41.

2763. H. Fujita, "Group Work of Microactuators," Intl. Advanced Robot Program Workshop on Micromachine Technologies and Systems, Tokyo, Japan, October 1993, pp. 24-31.

2764. Manabu Ataka, Akito Omodaka, Naohiro Takeshima, Hiroyuki Fujita, "Fabrication and operation of polyimide bimorph actuators for a ciliary motion system," J. Microelectromech. Syst. 2(December 1993):146-150.

2765. Y. Mita, S. Konishi, H. Fujita, "Two dimensional micro conveyance system with through holes for electrical and fluidic interconnection," Tech. Digest, 9th Intl. Conf. on Solid-State Sensors and Actuators (Transducers '97), Chicago, IL, 1997.

2766. Y. Mita, A. Kaiser, B. Stefanelli, P. Garda, M. Milgram, H. Fujita, "A distributed microactuator conveyance system with integrated controller," 1999 IEEE Intl. Conf. on Systems, Man and Cybernetics (SMC '99), 12-15 October 1999, Tokyo, Japan; http://www.ee.t.u-tokyo.ac.jp/~mita/SMC99/.

2767. K.F. Bohringer, B.R. Donald, R. Mihailovich, N.C. MacDonald, "A theory of manipulation and control for microfabricated actuator arrays," Proc. IEEE Workshop on Micro Electro Mechanical Systems (MEMS), Oiso, Japan, January 1994, pp. 102-107; http://www.cs.cornell.edu/home/karl/MicroActuators.

2768. K.F. Bohringer, B.R. Donald, R. Mihailovich, N.C. MacDonald, "Sensorless manipulation using massively parallel microfabricated actuator arrays," Proc. IEEE Intl. Conf. Robotics and Automation (ICRA), San Diego, CA, May 1994, pp. 826-833; http://www.cs.cornell.edu/home/karl/MicroManipulation.

2769. K.F. Bohringer, B.R. Donald, N.C. MacDonald, "Upper and lower bounds for programmable vector fields with applications to MEMS and vibratory plate parts feeders," in J.P. Laumond, M. Overmars, eds., Intl. Workshop on Algorithmic Foundations of Robotics (WAFR), Toulouse, France, July 1996, A.K. Peters, Wellesley, Mass., 1997, pp. 255-276; http://www.cs.cornell.edu/home/karl/MicroManipulation.

2770. Karl F. Bohringer, Bruce R. Donald, Noel C. MacDonald, Gregory T.A. Kovacs, John W. Suh, "Computational methods for design and control of MEMS micromanipulator arrays," IEEE Computational Science & Engineering 4(January-March 1997):17-29; http://www.cs.dartmouth.edu/~brd/cse97/cse97.html.

2771. Karl Fredrich Bohringer, John W. Suh, Bruce Randall Donald, Gregory T.A. Kovacs, "Vector fields for task-level distributed manipulation: experiments with organic micro actuator arrays," Proc. 1997 IEEE Intl. Conf. on Robotics and Automation (ICRA), Albuquerque, New Mexico, 20-25 April 1997, IEEE Robotics and Automation Society, pp. 1779-1786; http://www.ee.washington.edu/faculty/karl/Publications/ICRA97.pdf.

2772. K.F. Bohringer, B.R. Donald, N.C. MacDonald, "Programmable vector fields for distributed manipulation, with applications to MEMS actuator arrays and vibratory parts feeders," Intl. J. Robotics Research 18(February 1999):168-200; http://www.ee.washington.edu/faculty/karl/Publications/IJRR98.pdf.

2773. John W. Suh, R. Bruce Darling, Karl F. Bohringer, Bruce R. Donald, Henry Baltes, Gregory T.A. Kovacs, "CMOS integrated ciliary actuator array as a general-purpose micromanipulation tool for small objects," J. MEMS 8(December 1999):483-496; http://www.cs.dartmouth.edu/~brd/papers/jmems99.pdf or http://www.ee.washington.edu/faculty/karl/DistrManipulation/Papers/donald.pdf.

2774. Karl Friedrich Bohringer, Bruce Randall Donald, Lydia E. Kavraki, Florent Lamiraux, "Part orientation with one or two stable equilibria using programmable force fields," IEEE Trans. Robotics and Automation 16(April 2000):157-170; http://www-mtl.mit.edu/research/mems-salon/nick_fieldassemblyadvance.pdf.

2775. K.F. Bohringer, H. Choset, eds., Distributed Manipulation, Kluwer Academic Publishers, Norwell, MA, 2000; http://www.electrostatic.com/Bohringer.htm.

2776. J. Suh, R. B. Darling, K.F. Bohringer, H. Baltes, Bruce Randall Donald, G. Kovacs, "Fully programmable MEMS ciliary actuator arrays for micromanipulation tasks," IEEE Intl. Conf. on Robotics and Automation (ICRA) San Francisco, CA, April 2000, pp. 1101-1108; http://www.cs.dartmouth.edu/~brd/papers/karl-cmos-icra00.pdf.

2777. Karl Bohringer, Bruce Darling, Bruce Donald, Greg Kovacs, John Suh, "Micromanipulation with cilia arrays"; http://www.cs.dartmouth.edu/~brd/Research/MEMS/ciliaarrays.html.

2778. C. Liu, T. Tsai, Y.C. Tai, Peter Will, C.M. Ho, "A micromachined permalloy magnetic actuator array for micro robotics assembly systems," Tech. Digest, 8th Intl. Conf. on Solid-State Sensors and Actuators/Eurosensors IX (Transducers '95), Stockholm, Sweden, 25-29 June 1995, pp. 328-331.

2779. Peter Will, Wenheng Liu, "Parts manipulation on a MEMS intelligent motion surface," ISI Research Report ISI/RR-94-391, Marina del Rey, CA, May 1994.

2780. Wenheng Liu, Peter Will, "Parts manipulation on an intelligent motion surface," Human Robot Interaction and Cooperative Robots, Proc. IEEE/RSJ Intl. Conf. on Intell. Robots and Systems (IROS), Pittsburgh, PA, Vol. 3, August 1995, pp. 399-404.

2781. Wenheng Liu, Peter Will, Michael Pottenger, "Modeling and simulation of an intelligent motion surface in MEMS," First Intl. Conf. on Simulation and Design of Microsystems and Microstructures, Southampton, England, September 1995.

2782. Murilo G. Coutinho, Peter M. Will, P. Selvan Viswanathan, "The Intelligent Motion Surface: A hardware/software tool for the assembly of meso-scale devices," Proc. 1997 IEEE Intl. Conf. on Robotics and Automation, 20-25 April 1997, IEEE Robotics and Automation Society, pp. 1755-1760.

2783. Murilo Coutinho, Peter Will, "CILIA: a programmable, task-level planning, 2-D simulation software for arrays of manipulators," Intl. Workshop on Intelligent Robotics, Brasilia, Brazil, August 1997.

2784. Murilo G. Coutinho, Peter M. Will, "A general theory for positioning and orienting 2-D polygonal or curved parts using intelligent motion surfaces," Proc. IEEE Intl. Conf. on Robotics and Automation (ICRA), Leuven, Belgium, May 1998.

2785. J.W. Suh, S.F. Glander, R.B. Darling, C.W. Storment, G.T.A. Kovacs, "Combined organic thermal and electrostatic omnidirectional ciliary microactuator array for object positioning and inspection," Tech. Digest, Solid-State Sensors and Actuator Workshop, Hilton Head, SC, June 1996, pp. 168-173.

2786. J.W. Suh, S.F. Glander, R.B. Darling, C.W. Storment, G.T.A. Kovacs, "Organic thermal and electrostatic ciliary microactuator array for object manipulation," Sensors and Actuators A 58(1997):51-60.

2787. R.B. Darling, J.W. Suh, G.T.A. Kovacs, "Ciliary microactuatory array for scanning electron microscope positioning state," Vac. Sci. & Technol. A 16(1998):1998-2002.

2788. H. Nakazawa, Y. Watanabe, O. Morita, "The two-dimensional micro conveyor: Principles and fabrication process of the actuator," Tech. Digest, 9th Intl. Conf. on Solid-State Sensors and Actuators (Transducers '97), Chicago, IL, 1997.

2789. L. Kavraki, "Part orientation with programmable vector fields: two stable equilibria for most parts," Proc. IEEE Intl. Conf. Robotics and Automation (ICRA), Albuquerque, NM, April 1997.

2790. H. Nakazaw, Y. Wantanabe, O. Morita, M. Edo, E. Yonezawa, "The two-dimensional micro conveyer," Tech. Digest, 9th Intl. Conf. Solid-State Sensors and Actuators (Transducers'97), Chicago, IL, 16-19 June 1997, pp. 33-36.

2791. Thorbjorn Ebefors, Johan Ulfstedt Mattsson, Edvard Kelvesten, Goran Stemme, "A robust micro conveyor realized by arrayed polyimide joint actuators," Proc. 12th IEEE Intl. Micro Electro Mechanical System Conf. (MEMS'99), Orlando, FL, 17-21 January 1999, pp. 576-581; J. Micromech. Microeng. 10(2000):1-13; http://www.s3.kth.se/mst/research/publications/pdf/2000/tejm00preprint.pdf.

2792. Jonathan Luntz, William Messner, "Dynamics and control of discrete distributed manipulation," CCA 2001; http://lims.mech.nwu.edu/~lynch/cca2001/INV-CCA-5-4.pdf.

2793. T.D. Murphey, J.W. Burdick, "Smooth feedback control algorithms for distributed manipulators," Intl. Conf. on Robotics and Automation (ICRA), 2003; http://www.mech.nwu.edu/lims/people/murphey/murpheyicra2003b.pdf.

2794. R. Berger, H.P. Lang, E. Delamarche, Ch. Gerber, J.K. Gimzewski, C. Andreoli, J. Brugger, M. Despont, P. Vettiger, "Integration of silicon micromechanical arrays with molecular monolayers for miniaturized sensor systems," in A.T. Augousti, N.M. White, eds., Sensors and their Applications, Vol. 8, IOP, London, 1997, p. 71; http://monet.physik.unibas.ch/nose/rz2926.pdf.

2795. R. Berger, H.P. Lang, J.P. Ramseyer, F. Battiston, J.H. Fabian, L. Scandella, C. Andreoli, J. Brugger, M. Despont, P. Vettiger, E. Meyer, H.J. Guntherodt, Ch. Gerber, J.K. Gimzewski, "Transduction principles and integration of chemical sensors into a micromechanical array device," in A. van den Berg, P. Bergveld, eds., Sensor Technology in the Netherlands: State of the Art, Kluwer, Dordrecht, 1998, p. 33; http://monet.physik.unibas.ch/nose/rz2986.pdf.

2796. H.P. Lang, R. Berger, C. Andreoli, J. Brugger, M. Despont, P. Vettiger, Ch. Gerber, J.K. Gimzewski, J.P. Ramseyer, E. Meyer, H.J. Guntherodt, "Sequential position readout from arrays of micromechanical cantilever sensors," Appl. Phys. Lett. 72(19 January 1998):383-385; http://monet.physik.unibas.ch/~lang/pub/APL72383.pdf.

2797. H.P. Lang, R. Berger, C. Andreoli, J. Brugger, M. Despont, P. Vettiger, F. Battiston, J.P. Ramseyer, E. Meyer, T. Mezzacasa. L. Scandella, H.J. Guntherodt, Ch. Gerber, J.K. Gimzewski, "A chemical sensor based on a micromechanical cantilever array for the identification of gases and vapors," Appl. Phys. A 66(1998):S61-S64; http://www.chem.ucla.edu/dept/Faculty/gimzewski/pub/APA66S61.pdf.
2798. H.P. Lang, F.M. Battiston, M.K. Baller, R. Berger, J.P. Ramseyer, P. Fornaro, E. Meyer, H.J. Guntherodt, C. Andreoli, J. Brugger, M. Despont, P. Vettiger, J.H. Fabian, T. Mezzacasa, L. Scandella, Ch. Gerber, J.K. Gimzewski, "An electronic nose based on a micromechanical cantilever array" in D.J. Harrison, A. van den Berg, eds., Micro Total Analysis Systems, Kluwer, Dordrecht, 1999, pp. 57-60; http://monet.physik.unibas.ch/nose/UTAS.pdf.
2799. H.P. Lang, M.K. Baller, F.M. Battiston, J. Fritz, R. Berger, J.P. Ramseyer, P. Fornaro, E. Meyer, H.J. Guntherodt, J. Brugger, U. Drechsler, H. Rothuizen, M. Despont, P. Vettiger, Ch. Gerber, J.K. Gimzewski, "The nanomechanical NOSE," 12th IEEE Intl. Conf. on Micro Electro Mechanical Systems, 1999, pp. 9-13; http://www.chem.ucla.edu/dept/Faculty/gimzewski/pub/mems99.pdf.
2800. H.P. Lang, M.K. Baller, R. Berger, Ch. Gerber, J.K. Gimzewski, F.M. Battiston, P. Fornaro, J.P. Ramseyer, E. Meyer, H.J. Guntherodt, "An artificial nose based on a micromechanical cantilever array," Analytica Chimica Acta 393(1999):59-65; http://monet.unibas.ch/nose/rz3068.pdf.
2801. M.K. Baller, H.P. Lang, J. Fritz, Ch. Gerber, J.K. Gimzewski, U. Drechsler, H. Rothuizen, M. Despont, P. Vettiger, F.M. Battiston, J.P. Ramseyer, P. Fornaro, E. Meyer, H.J. Guntherodt, "A cantilever array based artificial nose," Ultramicroscopy 82(2000):1-9; http://monet.physik.unibas.ch/nose/ult821.pdf.
2802. F.M. Battiston, J.P. Ramseyer, H.P. Lang, M.K. Baller, Ch. Gerber, J.K. Gimzewski, E. Meyer, H.J. Guntherodt, "A chemical sensor based on a microfabricated cantilever array with simultaneous resonance-frequency and bending readout," Sensors and Actuators B 77(2001):122-131; http://monet.physik.unibas.ch/nose/battiston.pdf.
2803. B.H. Kim, F.E. Prins, D.P. Kern, S. Raible, U. Weimar, "Multicomponent analysis and prediction with a cantilever array based gas sensors," Sensors and Actuators B 78(2001):12-18.
2804. "Microcantilever Arrays," Protiveris Corp., 2003; http://www.protiveris.com/cantilever_tech/microcantileverarrays.html.
2805. Massood Tabib-Azar, Morton Litt, "Silicon wafer-scale micro-fabrication factory using scanning probe micro-robots," presentation at the Fifth Foresight Conference on Molecular Nanotechnology, 1997; http://www.foresight.org/Conferences/MNT05/Abstracts/Tabiabst.html.
2806. Seunghun Hong, Chad A. Mirkin, "A nanoplotter with both parallel and serial writing capabilities," Science 288(9 June 2000):1808-1811; http://www.nanotechnology.northwestern.edu/press/Science%20.Vol288.9june2000.pdf.
2807. Ming Zhang, David Bullen, Kee S. Ryu, Chang Liu, S. Hong, S. Chung, Chad Mirkin, "Passive and active probes for dip pen nanolithography," First IEEE Conference on Nanotechnology, 28-30 October 2001, Maui, HI; http://mass.micro.uiuc.edu/publications/papers/64.pdf.
2808. D. Bullen, M. Zhang, C. Liu, "Thermal-mechanical optimization of thermally actuated cantilever arrays," Smart Electronics, MEMS, and Nanotechnology Conference (4700), SPIE's 9th Annual International Symposium on Smart Structures and Materials, 17-21 March 2002, San Diego, CA; http://mass.micro.uiuc.edu/publications/papers/70.pdf.
2809. Ming Zhang, David Bullen, Sung-Wook Chung, Seunghun Hong, Kee S. Ryu, Zhifang Fan, Chad A. Mirkin, Chang Liu, "A MEMS nanoplotter with high-density parallel dip-pen nanolithography probe arrays," Nanotechnology 13(April 2002):212-217; http://mass.micro.uiuc.edu/publications/papers/72.pdf.
2810. X. Wang, D. Bullen, J. Zou, K. Ryu, C. Liu, S.W. Chung, C. Mirkin, "Linear probe arrays for dip-pen nanolithography," Intl. Conf. on Micro & Nano Systems (ICMNS 2002), 11-14 August 2002, Kunming, China; http://mass.micro.uiuc.edu/publications/papers/74.pdf.
2811. D. Bullen, S. Chung, X. Wang, J. Zou, C. Liu, Chad Mirkin, "Development of parallel dip pen nanolithography probe arrays for high throughput nanolithography," (Invited) Symposium LL: Rapid Prototyping Technologies, Materials Research Society Fall Meeting, Boston, MA, Proceedings of the MRS, Vol. 758, 2-6 December 2002; http://mass.micro.uiuc.edu/publications/papers/84.pdf.
2812. D. Bullen, X. Wang, J. Zou, S. Hong, S. Chung, K. Ryu, Z. Fan, C. Mirkin, C. Liu, "Micromachined arrayed dip pen nanolithography probes for sub-100 nm direct chemistry patterning," Proc. 16th IEEE International Micro Electro Mechanical Systems Conference, MEMS 2003, Kyoto, Japan, 19-23 January 2003; http://mass.micro.uiuc.edu/publications/papers/86.pdf.
2813. Jun Zou, David Bullen, Xuefeng Wang, Chang Liu, Chad A. Mirkin, "Conductivity-based contact sensing for probe arrays in dip-pen nanolithography," Appl. Phys. Lett. 83(2003):581.
2814. S. Martel, S. Riebel, T. Koker, M. Sherwood, I. Hunter, "Large-scale nanorobotic factory automation based on the NanoWalker technology," Proceedings of the 8th IEEE International conference on Emerging Technologies and Factory Automation, Special Session on Microrobotics in Manufacturing, Nice, France, Oct. 15-18, 2001.
2815. S. Martel, I. Hunter, "Nanofactories based on a fleet of scientific instruments configured as miniature autonomous robots," Proceedings of the 3rd International Workshop on Microfactories, Minneapolis, MN, USA, pp.97-100, Sept. 16-18, 2002.
2816. S. Martel, A. Schindler, G. Baumann, S. Riebel, T. Boitani, "Cooling platform for an automated nanofactory based on a fleet of miniature robots designed for atomic scale operations," IEEE Automation 2003, Taiwan, May 8-11, 2003.
2817. S. Martel, I. Hunter, "Nanofactories based on a fleet of scientific instruments configured as miniature autonomous robots," Journal of Micromechatronics, 2003, in press.
2818. S. Martel, T. Koker, S. Riebel, M. Sherwood, J. Suurkivi, I. Hunter, "An infrastructure suited for supporting a fleet of wireless miniature robots designed for atomic-scale operations," Proceedings of SPIE: Microrobotics and Microassembly, Vol. 4568, pp. 221-230, Newton, MA, Oct. 29-31, 2001.
2819. "CimStation Robotics," Applied Computing & Engineering Ltd., 8/11/2003; http://www.sgi.com/products/appsdirectory.dir/irix/products/c/935500.html.
2820. Deneb Robotics, Inc., "IGRIP and Ultra Products," 2003; http://www.deneb.com/products/igrip.html.
2821. "Simulation Software: MotoSim," MotoMan, a Yaskawa Company, 2004; http://www.motoman.com/products/software/simulation.htm.
2822. "WorkSpace 5, The Next Generation Robotic Simulation Software," 2004; http://www.workspace5.com.
2823. "Cyberbotics: Professional Mobile Robot Simulation," 18 February 2004; http://www.cyberbotics.com.
2824. Deneb Robotics, Inc., "Design for Deneb/ASSEMBLY (DFA)," 2003; http://www.deneb.com/products/assembly.html.
2825. "Flexsim Simulation Software," 18 February 2004; http://www.flexsim.com.
2826. "ShowFlow Simulation Software," 2004; http://www.showflow.co.uk.
2827. "SimCAD Process Simulator," 2004; http://www.simcadpro.com.
2828. Ron Knott, "Fibonacci Numbers and Nature," 10 April 2003; http://www.mcs.surrey.ac.uk/Personal/R.Knott/Fibonacci/fibnat.html.
2829. Leonardo Fibonacci, Liber Abbaci (The Book of the Abacus), 1202, revised 1228.
2830. D. Harkin, "On the mathematical works of Francois Edouard Anatole Lucas," Enseignement Mathematique 3(1957):276-288.
2831. M.R. Williams, "Edouard Lucas vindicated," Ann. Hist. Comput. 6(1984):404.
2832. Francois Edouard Anatole Lucas; http://www-groups.dcs.st-and.ac.uk/~history/Mathematicians/Lucas.html.
2833. S.L.Basin, "The Fibonacci sequence as it appears in Nature," Fibonacci Quarterly 1(January-February 1963):53-57.
2834. Basil Davis, "Fibonacci numbers in physics," Fibonacci Quarterly 10(November-December 1972):659.
2835. A. Girard, L'Arithmetique de Simon Steven de Bruges, Leiden, 1634.
2836. H.S.M. Coxeter, "The golden section, phyllotaxis, and Whythoff's game," Ser. Math. 19(1953):135.
2837. Donald Ervin Knuth, "Section 1.2.8 Fundamental Algorithms," Volume 1, The Art of Computer Programming, Third Edition, Addison-Wesley Publishing Co., 1997.
2838. Ron Knott, "A formula for Fib(n)," 27 August 2001; http://www.mcs.surrey.ac.uk/Personal/R.Knott/Fibonacci/fibFormula.html.

2839. Sarah E. Anderson, Gerard E. Dallal, Aviva Must, "Relative weight and race influence average age at menarche: Results from two nationally representative surveys of U.S. girls studied 25 years apart," Pediatrics 111(April 2003):844-850; http://pediatrics.aappublications.org/cgi/content/abstract/111/4/844. See also: M.D. Lemonick, "Teens before their time," Time 156(30 October 2000):64-74; http://www.cys-community.org/CYSnew1.html; "Periods," Palo Alto Medical Foundation," 2004; http://www.pamf.org/teen/health/femalehealth/periods/early.html.
2840. P.H. Whincup, J.A. Gilg, K. Odoki, S.J. Taylor, D.G. Cook, "Age of menarche in contemporary British teenagers: survey of girls born between 1982 and 1986," BMJ 322(5 May 2001):1095-1096, BMJ 323(18 August 2001):398 (comment); http://www.ncpa.org/pi/enviro/pd050401c.html.
2841. Harry Finley, "Average age at menarche in various cultures," 2003; http://www.mum.org/menarage.htm.
2842. Alain J. Phares, Kim H. Simmons, "Fibonacci numbers revisited: A combinatorics function point of view," Am. J. Phys. 48(February 1980):159-162.
2843. Blaise Pascal, Traite du triangle arithmetique, 1654. See also: A.W.F. Edwards, Pascal's Arithmetical Triangle: The Story of a Mathematical Idea, Johns Hopkins University Press, 2002. Online resources (April 2003): "Wolfram Research: Pascal's Triangle," http://mathworld.wolfram.com/PascalsTriangle.html; "Math Forum: Pascal's Triangle," http://mathforum.org/workshops/usi/pascal/; "Introduction to Pascal's Triangle," http://www.krysstal.com/binomial.html; "Pascal's Triangle and Its Patterns," http://ptri1.tripod.com/#polygonal.
2844. Graham Kennedy, "Tribbles," 1998; http://www.ditl.org/index.htm?daybody=/species/dattribbles.htm.
2845. V.E. Hoggatt, Jr., D.A. Lind, "The dying rabbit problem," Fibonacci Quarterly 7(September-October 1969):482-487.
2846. C. Kittle, Introduction to Solid State Physics, Chapter 2, John Wiley and Sons, New York, 1956.
2847. Thomas Malthus, "An Essay on the Principle of Population, as it Affects the Future Improvement of Society with Remarks on the Speculations of Mr. Godwin, M. Condorcet, and Other Writers," printed for J. Johnson, in St. Paul's Church-Yard, London, 1798; http://www.ac.wwu.edu/~stephan/malthus/malthus.0.html.
2848. E. Szathmary, I. Gladkih, "Sub-exponential growth and coexistence of non-enzymatically replicating templates," J. Theor. Biol. 138(1989):55-58.
2849. G. von Kiedrowski, B. Wlotzka, J. Helbing, M. Matzen, S. Jordan, "Parabolic growth of a hexadeoxynucleotide bearing a 3'-5'-phosphoramidate bond," Angew. Chem. Int. Ed. Engl. 30(1991):423-426 (1991), ibid. 30(1991):892.
2850. E. Szathmary, "Simple growth laws and selection consequences," Trends Ecol. Evol. 6(1991):366-370.
2851. G. von Kiedrowski, "Minimal replicator theory I: Parabolic vs. exponential growth," Bioorganic Chemistry Frontiers 3(1993):113-146.
2852. Z. Varga, E. Szathmary, "An extremum principle for parabolic competition," Bull. Math. Biol. 59(1997):1145-1154.
2853. G. von Kiedrowski, E. Szathmary, "Selection versus coexistence of parabolic replicators spreading on surfaces," Selection 1(2000):173-179.
2854. I. Scheuring, E. Szathmary, "Survival of replicators with parabolic growth tendency and exponential decay," J. Theor. Biol. 212(2001):99-105.
2855. G. Meszena, E. Szathmary, "The adaptive dynamics of parabolic replicators," Selection 2(2001):147-159; http://angel.elte.hu/~geza/FEJ-10.PDF.
2856. A.J. Lotka, Elements of Physical Biology, Williams & Wilkins Co., Baltimore, 1925; V. Volterra, Variazioni e fluttuazioni del numero d'individui in specie animali conviventi, Mem. R. Accad. Naz. dei Lincei. Ser. VI, Vol. 2, 1926.
2857. D.A. MacLulich, "Fluctuations in the numbers of the varying hare *(Lepus americanus),"* University of Toronto Studies, Biology Series, No. 43, 1937.
2858. A.M. Zamamiri, G. Birol, M.A. Hjortso, "Multiple stable states and hysteresis in continuous, oscillating cultures of budding yeast," Biotechnol. Bioeng. 75(5 November 2001):305-312; G. Birol, A.M. Zamamiri, M.A. Hjortso, "Frequency analysis of autonomously oscillating yeast cultures," Process Biochem. 35(1 July 2000):1085-1091; M.J. Kurtz, G.Y. Zhu, A.M. Zamamiri, M.A. Henson, M.A. Hjortso, "Control of oscillating microbial cultures described by population balance models," Ind. Eng. Chem. Res. 37(1998):4059-4070.
2859. Edward B. Radcliffe, "Introduction to Population Ecology," Department of Entomology, University of Minnesota, 20 June 2000; http://www.ipmworld.umn.edu/chapters/ecology.htm.
2860. Alexei Sharov, "Quantitative population ecology," On-Line Lectures, Department of Entomology, Virginia Tech, Blacksburg, VA, 9 September 1996; http://www.gypsymoth.ento.vt.edu/~sharov/PopEcol/popecol.html and http://www.gypsymoth.ento.vt.edu/~sharov/popechome/welcome.html.
2861. George Evelyn Hutchinson, An Introduction to Population Ecology, Yale University Press, New Haven, CT, 2000.
2862. Russell Lande, Steinar Engen, Bernt-Erik Saether, Stochastic Population Models in Ecology and Conservation: An Introduction, Oxford University Press, New York, 2003.
2863. John H. Vandermeer, Deborah E. Goldberg, Population Ecology: First Principles, Princeton University Press, Princeton, NJ, 2003.
2864. Paul B. Rainey, Katrina Rainey, "Evolution of cooperation and conflict in experimental bacterial populations," Nature 425(4 September 2003):72-74.
2865. R.H. MacArthur, E.O. Wilson, The Theory of Island Biogeography, Princeton University Press, Princeton, NJ, 1967.
2866. M.D. Mountford, "Population survival in a variable environment," J. Theor. Biol. 32(July 1971):75-79.
2867. Herbert A. Simon, The Sciences of the Artificial, 3rd edition, MIT Press, Cambridge, MA, 1996.
2868. J. Storrs Hall, "Recent results in SRMS," Foresight Update #53, January 2004, pp. 10, 12.
2869. Piet Hut, "The GRAPE-4, a teraflops stellar dynamics computer," 28 April 1997; http://arxiv.org/pdf/astro-ph/9704277.
2870. Feng-Hsiung Hsu, Behind Deep Blue: Building the Computer that Defeated the World Chess Champion, Princeton University Press, Princeton, NJ, 2002.
2871. John Markoff, "Computing's Big Shift: Flexibility in the Chips," The New York Times, 16 June 2003; http://www.nytimes.com/2003/06/16/technology/16CHIP.html.
2872. Paul Armer, "Attitudes toward intelligent machines," Symposium on Bionics, Wadd Technical Report 60/600, 1960, pp. 13-19. Reprinted in Edward A. Feigenbaum, Julian Feldman, Computers and Thought; McGraw-Hill Book Co., Inc., New York, 1963, pp. 389-405.
2873. James T. Culbertson, The Minds of Robots, University, University of Illinois Press, Urbana, IL, 1963.
2874. C.R. Evans, A.D.J. Robertson, eds., Cybernetics, University Park Press, Baltimore, MD, 1968.
2875. Gheorghe Cosma, Octavian Cosma, "The subconscious of computers," Cybernetica 17(1974):157-176.
2876. Terry Winograd, "Artificial intelligence: When will computers understand people?" Psychology Today 7(May 1974):73-79.
2877. F.H. George, J.D. Humphries, eds., The Robots are Coming, National Computing Centre Ltd., Sandbach, Cheshire, England, 1974.
2878. Donald Michie, On Machine Intelligence, John Wiley & Sons, New York, 1974.
2879. Bertram Raphael, The Thinking Computer: Mind Inside Matter, W.H. Freeman & Co., San Francisco, 1976.
2880. Philip C. Jackson, Introduction to Artificial Intelligence, Second Edition, Dover Publications, New York, 1985.
2881. Jacques Ferber, Multi-Agent Systems: An Introduction to Distributed Artificial Intelligence, Addison-Wesley, Reading, MA, 1999.
2882. James Kennedy, Russell C. Eberhart, Swarm Intelligence, Academic Press, San Diego, CA, 2001.
2883. Stuart J. Russell, Peter Norvig, Artificial Intelligence: A Modern Approach, Second Edition, Prentice Hall, New York, 2002.
2884. Hans Moravec, Mind Children: The Future of Robot and Human Intelligence, Harvard University Press, Cambridge, MA, 1988.
2885. Frank J. Tipler, The Physics of Immortality, Doubleday, New York, 1994.
2886. Robert A. Freitas Jr., "The future of computers," Analog 116(March 1996):57-73. (Manuscript accepted for publication, 12 April 1995.) http://www.rfreitas.com/Nano/TheFutureOfComputers—Analog—March1996.htm.
2887. Raymond Kurzweil, The Age of Spiritual Machines, Viking Press, New York, 1999.
2888. Arthur C. Clarke, Profiles of the Future, Bantam Books (Harper & Row Publishers), New York, 1962.
2889. A.C. Clarke, Report on Planet Three, Harper & Row, New York, 1972.

2890. Carl Sagan, "In Praise of Robots," Natural History 84(January 1975):8-20.

2891. Douglas Mulhall, Our Molecular Future: How Nanotechnology, Robotics, Genetics and Artificial Intelligence Will Transform Our World, Prometheus Books, 2002.

2892. Isaac Asimov, I, Robot, Gnome Press, 1950; reprinted by Doubleday, Garden City, New York, 1963.

2893. Isaac Asimov, "The Last Question," Columbia Publications, 1956; http://jhu.simon.rochester.edu/public_html/writing-others/last-question.htm.

2894. Arthur C. Clarke, 2001: A Space Odyssey, Signet Books, New York, 1968.

2895. James P. Hogan, The Two Faces of Tomorrow, Ballantine Books, New York, 1979.

2896. Greg Bear, "Blood Music," Analog 103(June 1983):12-36; Greg Bear, Blood Music, William Morrow & Co., New York, 1985.

2897. "The New Breed," Outer Limits (TV show), 1996; http://www.theouterlimits.com/episodes/season1/112.htm.

2898. Michael Crichton, Prey, HarperCollins Publishers, New York, 2002.

2899. Steven B. Harris, "The return of the Krell machine: nanotechnology, the singularity, and the empty planet syndrome," Gerontology Research Group, Charter Section, 2002; http://www.grg.org/charter/Krell.htm.

2900. Sam Williams, Arguing A.I.: The Battle for Twenty-First Century Science, Random House Trade Paperbacks, New York, 2002; http://www.amazon.com/exec/obidos/tg/detail/-/081299180X/.

2901. Richard Brook Cathcart, "Geological time termination of a SciFi biosphere: An alternative view of The Forbidden Planet," GEOGRAPHOS, 2002; http://www.daviddarling.info/encyclopedia/F/ForbPlan_Cathcart.html.

2902. Martin J. Rees, Our Final Hour. A Scientist's Warning: How Terror, Error, and Environmental Disaster Threaten Humankind's Future In This Century — On Earth and Beyond, Basic Books, New York, 2003.

2903. Bill McKibben, Enough: Staying Human in an Engineered Age, Times Books, New York, 2003.

2904. Tim Radford, "Brave new world or miniature menace? Why Charles fears grey goo nightmare. Royal Society asked to look at risks of nanotechnology," The Guardian, Tuesday, 29 April 2003; http://www.guardian.co.uk/Print/0,3858,4657361,00.html. See also: "Self-replicating Microscopic Robots Concern Prince Charles," BetterHumans, 29 April 2003; http://www.betterhumans.com/News/news.aspx?articleID=2003-04-29-1. Subsequent denial of gray goo fears by Prince Charles: John-Paul Ford Rojas, "Charles reignites debate over cutting edge science," PA News, 11 July 2004; http://news.scotsman.com/latest.cfm?id=3188068; see also. http://www.theinquirer.net/?article=17153.

2905. Lee-Anne Broadhead, Sean Howard, "The Heart of Darkness," Resurgence #221, November/December 2003; http://resurgence.gn.apc.org/issues/broadhead221.htm.

2906. Marshall Brain, "Robotic Nation," 2003; http://marshallbrain.com/robotic-nation.htm. See also: Joanna Glasner, "How Robots Will Steal Your Job," Wired, 5 August 2003; http://www.wired.com/news/business/0,1367,59882,00.html.

2907. Thomas M. Georges, Digital Soul: Intelligent Machines and Human Values, Westview Press, 2003; http://www.amazon.com/exec/obidos/tg/detail/-/0813340578/.

2908. Bill Joy, "Why the future doesn't need us," Wired 8(April 2000); http://www.wired.com/wired/archive/8.04/joy.html. Response by Ralph Merkle, "Text of prepared comments by Ralph C. Merkle at the April 1, 2000 Stanford Symposium organized by Douglas Hofstadter," at: http://www.zyvex.com/nanotech/talks/stanford000401.html.

2909. Robert A. Freitas Jr., "Some Limits to Global Ecophagy by Biovorous Nanoreplicators, with Public Policy Recommendations," Zyvex preprint, April 2000; http://www.foresight.org/NanoRev/Ecophagy.html.

2910. K. Eric Drexler, Chris Peterson, Gayle Pergamit, Unbounding the Future: The Nanotechnology Revolution, William Morrow/Quill Books, NY, 1991; http://www.foresight.org/UTF/Unbound_LBW/.

2911. Nick Bostrom, "Existential Risks: Analyzing Human Extinction Scenarios," J. Evolution and Technology 9(2000); http://www.nickbostrom.com/existential/risks.html.

2912. Ralph C. Merkle, "Energy Limits to the Computational Power of the Human Brain," Foresight Update, No. 6, August 1989; http://www.merkle.com/brainLimits.html.

2913. Jacob T. Schwartz, "The new connectionism: Developing relationships between neuroscience and artificial intelligence," in Stephen R. Graubard, ed., The Artificial Intelligence Debate, MIT Press, Cambridge, MA, 1990.

2914. Nick Bostrom, "How Long Before Superintelligence?" Intl. J. Futures Studies 2(1998); http://www.nickbostrom.com/superintelligence.html.

2915. Thomas K. Landauer, "How much do people remember? Some estimates of the quantity of learned information in long-term memory," Cognitive Science 10(1986):477-493.

2916. Ralph C. Merkle, "How Many Bytes in Human Memory?" Foresight Update, No. 4, October 1988; http://www.merkle.com/humanMemory.html.

2917. Christopher Cherniak, "The bounded brain: Toward quantitative neuroanatomy," J. Cognitive Neuroscience 2(1990):58-68.

2918. Pierre Baldi, The Shattered Self: The End of Natural Evolution, MIT Press, Cambridge, MA, 2001.

2919. John von Neumann, The Computer and the Brain, Yale University Press, New Haven, CT, 1958.

2920. Yingxu Wang, Dong Liu, Ying Wang, "Discovering the Capacity of Human Memory," Brain and Mind 4(August 2003):189-198.

2921. Carl Sagan, ed., Communication with Extraterrestrial Intelligence (CETI), MIT Press, Cambridge, MA, 1973.

2922. Marvin Minsky, personal communication to Robert A. Freitas Jr., 30 July 2003.

2923. Marvin Minsky, Semantic Information Processing, MIT Press, 1968.

2924. Nicholas Wade, "Genetic Analysis Yields Intimations of a Primordial Commune," New York Times, 13 June 2000; http://www.nytimes.com/library/national/science/061300sci-life-origins.html.

2925. Stephen J. Mojzsis, Gustaf Arrhenius, Kevin D. McKeegan, T. Mark Harrison, Allen P. Nutman, Clark R. Friend, "Evidence for life on Earth before 3,800 million years ago," Nature 384(7 November 1996):55-59, 21-22 (comment); Nature 386(17 April 1997):665 (erratum). See also: "Life On Earth Began At Least 3.85 Billion Years Ago, 400 Million Years Earlier Than Previously Thought, Scientists Say," NASA News Release, Release No. 96-230, 6 November 1996; http://www.fas.org/mars/nn961106.htm.

2926. Christopher M. Fedo, Martin J. Whitehouse, "Metasomatic origin of quartz-pyroxene rock, Akilia, Greenland, and implications for Earth's earliest life," Science 296(24 May 2002):1448-1452. See also: Ben Harder, "New Analysis Throws Age of Life on Earth Into Doubt," National Geographic News, 23 May 2002, http://news.nationalgeographic.com/news/2002/05/0523_020523_rocks.html; Kenneth Chang, "Dusted for Life's Fingerprints, Rocks Fail," New York Times, 4 June 2002, http://www.nytimes.com/2002/06/04/science/04ROCK.html.

2927. Richard G. Klein, The Dawn of Human Culture, John Wiley & Sons, New York, 2002. See also: Charles Darwin, The Descent of Man, 1871; http://www.infidels.org/library/historical/charles_darwin/descent_of_man/index.shtml.

2928. Ralph C. Merkle, "Self replication and nanotechnology," see at: http://www.zyvex.com/nanotech/selfRep.html.

2929. "NIH Guidelines for Research Involving Recombinant DNA Molecules," January 1996 revision, see at: http://www.ehs.psu.edu/biosafety/nih/nih95-1.htm.

2930. Heifer International website; http://www.heifer.org/.

2931. Michael Williams, "The Mind Machine," 1919. Cited by H. Bruce Franklin, "Computers in fiction," Encyclopedia of Computer Science, Nature Publishing Group, 2000; http://newark.rutgers.edu/~hbf/compulit.htm.

2932. Joseph Everidge Kelleam, "Rust," Astounding Science Fiction, October 1939. See cover art at http://www.frankwu.com/Paul-13.11.html.

2933. Eric Frank Russell, "Mechanistra," Astounding Science Fiction, January 1942.

2934. Freeman J. Dyson, "The World, The Flesh, and the Devil. V. Self-Reproducing Machinery," Third J.D. Bernal Lecture at Birkbeck College, London, U.K., on 16 May 1972; Birkbeck College private printing, 1972. Reprinted as "Appendix D" in Carl Sagan, ed., Communication with Extraterrestrial Intelligence (CETI), MIT Press, Cambridge, MA, 1973; http://impearls.blogspot.com/2002_11_10_impearls_archive.html#84391106.

2935. James Paul Wesley, Ecophysics: The Application of Physics to Ecology, Charles C. Thomas, Publisher, Springfield, Illinois, 1974.

2936. Fred Saberhagen, Berserker's Planet, Tor Books, New York, 1975; Fred Saberhagen, Berserker's Planet, Ace Books, 1984 and Tor Books, 1991. See cover art at http://www.berserker.com/bk_berserkersplanet.htm.

2937. Frank Honywill George, Machine Takeover: The Growing Threat to Human Freedom in a Computer-Controlled Society, Pergamon Press, Oxford, 1976; New York, 1977.

2938. Langdon Winner, Autonomous Technology: Technics-Out-Of-Control As A Theme In Political Thought, MIT Press, Cambridge, MA, 1977.
2939. Kevin Warwick, March of the Machines: Why the New Race of Robots Will Rule the World, Century Books, Evergreen, CO, 1997.
2940. Raymond Kurzweil, The Singularity is Near, Viking Press, New York, 2005.
2941. David Forrest, "Regulating Nanotechnology Development," Foresight Institute website, 23 March 1989; http://www.foresight.org/NanoRev/Forrest1989.html.
2942. http://www.foresight.org/guidelines/current.html#Preamble and http://www.foresight.org/guidelines/current.html#Background.
2943. Freeman J. Dyson, personal communication to Robert A. Freitas Jr., 5 August 2003.
2944. "Foresight Publishes Guidelines for Development of Nanotechnology," Foresight Institute Press Release, 14 June 2000; http://www.foresight.org/guidelines/pr001.html.
2945. "Bioethics Statement of Principles," Biotechnology Industry Organization, 2003; http://www.bio.org/bioethics/principles.asp.
2946. "Our Bioethics Policy," Egea Biosciences, Inc., 2003; http://www.egeabiosciences.com/Bioethics.htm.
2947. The Aspen Institute; http://www.aspeninstitute.org.
2948. Christine Peterson, "Molecular Manufacturing: Societal Implications of Advanced Nanotechnology," 9 April 2003; http://www.kurzweilai.net/meme/frame.html?main=/articles/art0557.html.
2949. Ray Kurzweil, "Testimony of Ray Kurzweil on the Societal Implications of Nanotechnology," 9 April 2003; http://www.kurzweilai.net/meme/frame.html?main=/articles/art0556.html.
2950. "H.R. 766. An Act To provide for a National Nanotechnology Research and Development Program, and for other purposes," 108th Congress, 1st Session, 8 May 2003; http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:h766ih.txt.pdf or http://www.theorator.com/bills108/hr766.html (early versions).
2951. "S. 189. 21st Century Nanotechnology Research and Development Act," 108th Congress, 1st Session, 22 June 2003.
2952. S.B. 189, "Section 5(b) Study on Molecular Self-Assembly," 21st Century Nanotechnology Research and Development Act, 2003; http://www.smalltimes.com/smallstage/images/nanobills189.pdf.
2953. Glenn Reynolds, "Give Thanks for Small Victories," Tech Central Station, 26 November 2003; http://techcentralstation.com/112603B.html.
2954. Mitch Waldrop, "NSF awards new grants to study social implications of nanotechnology," National Science Foundation, 25 August 2003; http://www.eurekalert.org/pub_releases/2003-08/nsf-nan082503.php.
2955. Loren Knapp, personal communication to Robert A. Freitas Jr., 30 September 2003.
2956. Zyvex Corp., Richardson TX; http://www.zyvex.com.
2957. J. Moffet, "Environmental priority setting based on comparative risk and public input," Canadian Public Administration 39(1996):362-385.
2958. V. Covello, "Risk comparisons and risk communication: Issues and problems in comparing health and environmental risks," in R.E. Kasperson, P.J.M. Stallen, eds., Communicating Risks to the Public: International Perspectives, Kluwer Academic Publishers, Dordrecht, 1992, pp. 79-124.
2959. David S. Goodsell, Bionanotechnology: Lessons from Nature, John Wiley & Sons, New York, 2004.
2960. Murray Leinster, The Duplicators, Ace Books, New York, 1964. Originally published as "The Lost Race," Thrilling Wonder Stories, April 1949.
2961. Gerald D. Nordley, "On the socioeconomic impact of smart self-replicating machines," CONTACT 2000, NASA/Ames Research Center; http://www.contact-conference.com/archive/00.html.
2962. V. Weil, "Ethical Issues in Nanotechnology," in M.C. Roco, W.S. Bainbridge, eds., Societal Implications of Nanoscience and Nanotechnology, Kluwer, Dordrecht, 2001, pp. 193-198; R.H. Smith, "Social, Ethical, and Legal Implications of Nanotechnology," in M.C. Roco, W.S. Bainbridge, eds., Societal Implications of Nanoscience and Nanotechnology, Kluwer, Dordrecht, 2001, pp. 203-211. See also http://itri.loyola.edu/nano/societalimpact/nanosi.pdf.
2963. "Task Area 3: Problems of Self-replication, Risk, and Cascading Effects in Nanotechnology: Analogies between Biological Systems and Nanoengineering," in Philosophical and Social Dimensions of Nanoscale Research — From Laboratory to Society: Developing an Informed Approach to Nanoscale Science and Technology, Working Group for the Study of the Philosophy and Ethics of Complexity and Scale [SPECS], University of South Carolina NanoCenter, 17 March 2003; http://www.cla.sc.edu/cpecs/nirt/nirt.html.
2964. Frederick A. Fiedler, Glenn H. Reynolds, "Legal Problems of Nanotechnology: An Overview," Southern California Interdisciplinary Law Journal 3(1994):593-629.
2965. Ty S. Wahab Twibell, "Nano law: The legal implications of self-replicating nanotechnology," Nanotechnology Magazine, 2000; http://www.irannano.org/English/publication/Articles/Nano-law.htm.
2966. John Miller, "Beyond Biotechnology: FDA Regulation Of Nanomedicine," Columbia Science and Technology Law Review, Vol. IV, 2002-2003; http://www.stlr.org/html/volume4/miller.pdf.
2967. Glenn Harlan Reynolds, "Nanotechnology and regulatory policy: three futures," Harv. J. Law & Technol. 17(Fall 2003); http://instapundit.com/lawrev/HJOLTnano.pdf.
2968. "Milestones in Medical Research," Eli Lilly; http://www.lilly.com/about/milestones.html.
2969. B.A. Pfeifer, S.J. Admiraal, H. Gramajo, D.E. Cane, Chaitan Khosla, "Biosynthesis of complex polyketides in a metabolically engineered strain of E. coli," Science 291(2 March 2001):1790-1792, 1683 (comment).
2970. "L-Salivarius Plus Other Beneficial Microflora," Product Information Sheet No. 8058, Life Plus, 1996, at http://www.lightplus.com/lifeplus/8058.html; "Life Plus Vitamin/Herbal Answer For a Healthy Digestive Tract," at http://members.aol.com/probb0254/salivrex.html; "Support Digestion Naturally: Salivarex," at http://www.healthyway.net/products/digestion.htm.
2971. "Alkadophilus: The Non-Refrigerated Acidophilus," at: http://www.morter.com/HTML-FILES/ALKAdophilus.HTM, http://www.backcare-center.com/NC-AlkaLine.htm, and http://www.nutritionforhealth.com/herbalformulas.htm.
2972. Michael G. Kaplitt, Arthur D. Loewy, eds., Viral Vectors: Gene Therapy and Neuroscience Applications, Academic Press, New York, 1995.
2973. Angel Cid-Arregui, Alejandro Garcia-Carranca, eds., Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co., 2000.
2974. David Latchman, Viral Vectors for Treating Diseases of the Nervous System, Academic Press, New York, 2003.
2975. Curtis A. MacHida, Jules G. Constant, eds., Viral Vectors for Gene Therapy: Methods and Protocols, Humana Press, 2003.
2976. P. Kotrba, L. Doleckova, V. de Lorenzo, T. Ruml, "Enhanced bioaccumulation of heavy metal ions by bacterial cells due to surface display of short metal binding peptides," Appl. Environ. Microbiol. 65(March 1999):1092-1098; http://aem.asm.org/cgi/content/full/65/3/1092?view=full&pmid=10049868.
2977. W. Bae, R.K. Mehra, A. Mulchandani, W. Chen, "Genetic engineering of Escherichia coli for enhanced uptake and bioaccumulation of mercury," Appl. Environ. Microbiol. 67(November 2001):5335-5338; http://aem.asm.org/cgi/content/full/67/11/5335?view=full&pmid=11679366.
2978. X. Deng, Q.B. Li, Y.H. Lu, D.H. Sun, Y.L. Huang, X.R. Chen, "Bioaccumulation of nickel from aqueous solutions by genetically engineered Escherichia coli," Water Res. 37(May 2003):2505-2511.
2979. Joseph Henry Press, "Chapter 5. Biotechnology and the Environment," Biotechnology Unzipped: Promises and Realities, National Academy of Sciences, Washington, DC, 2003, pp. 134-160; http://books.nap.edu/books/0309057779/html/134.html.
2980. I. Suzuki, "Microbial leaching of metals from sulfide minerals," Biotechnol. Adv. 19(1 April 2001):119-132.
2981. D.V. Rao, C.T. Shivannavar, S.M. Gaddad, "Bioleaching of copper from chalcopyrite ore by fungi," Indian J. Exp. Biol. 40(March 2002):319-324.
2982. D.E. Rawlings, D. Dew, C. du Plessis, "Biomineralization of metal-containing ores and concentrates," Trends Biotechnol. 21(January 2003):38-44.
2983. G.J. Olson, J.A. Brierley, C.L. Brierley, "Bioleaching review part B: progress in bioleaching: applications of microbial processes by the minerals industries," Appl. Microbiol. Biotechnol. 63(December 2003):249-257.
2984. Ananda M. Chakrabarty, "Microorganisms having multiple compatible degradative energy-generating plasmids and preparation thereof," United States Patent No. 4,259,444, 31 March 1981; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,259,444.WKU.&OS=PN/4,259,444&RS=PN/4,259,444.
2985. Ananda M. Chakrabarty, Scott T. Kellogg, "Bacteria capable of dissimilation of environmentally persistent chemical compounds," United States Patent No. 4,535,061, 13 August 1985; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,535,061.WKU.&OS=PN/4,535,061&RS=PN/4,535,061.

2986. Saw-Wai Hla, Karl-Heinz Rieder, "STM control of chemical reactions: single-molecule synthesis," Annu. Rev. Phys. Chem. 54(2003):307-330.

2987. Farrington Daniels, Robert A. Alberty, Physical Chemistry, Third Edition, John Wiley & Sons, New York, 1966.

2988. David Birch, The King's Chessboard, Dial Books, New York, 1988.

2989. David Barry, The Rajah's Rice: A Mathematical Folktale from India, W.H. Freeman and Co., New York, 1994.

2990. Hitz Demi, One Grain of Rice: A Mathematical Folktale, Scholastic, 1997.

2991. "Table No. 828. Selected Farm Products — United States and World Production and Exports: 1995 to 2002," Agriculture, Statistical Abstract of the United States: 2003, U.S. Census Bureau, 2004, p. 546; http://www.census.gov/prod/2004pubs/03statab/agricult.pdf.

2992. Helena Claire Pittman, A Grain of Rice, Hastings House Publishers, New York, 1986.

2993. Charles Babbage, Reflections on the Decline of Science in England and on Some of Its Causes, B. Fellowes, London, 1830.

2994. Harry D. Truman, Memoirs, Volume I: Year of Decisions, Doubleday and Co., Inc., Garden City, 1955, p. 11.

2995. William D. Leahy, I Was There, Whittlesey House, McGraw-Hill Book Company, New York, 1950.

2996. Joann Muller, "7 Digital 7," Forbes 173(21 June 2004):117-120.

3000. "Nanotechnology: Drexler And Smalley Make The Case For And Against 'Molecular Assemblers'," Chemical and Engineering News 81(1 December 2003):37-42; http://pubs.acs.org/cen/coverstory/8148/8148counterpoint.html. See also: letters on the debate in C&EN, 26 January 2004.

3001. Neil Jacobstein, "Nanotechnology Research and Development Sponsorship," in Markus Krummenacker, James Lewis, eds., Prospects in Nanotechnology: Toward Molecular Manufacturing, John Wiley & Sons, New York, 1995, pp. 207-220.

3002. David R. Myers, Carol W. Sumpter, Steven T. Walsh, Bruce A. Kirchhoff, "A practitioner's view: Evolutionary stages of disruptive technologies," IEEE Trans. Eng. Management 49(November 2002):322-329.

3003. John M. Michelsen, Mark J. Dyer, Jim Von Ehr, "Assembler construction by proximal probe," paper presented at the Fifth Foresight Conference on Molecular Nanotechnology, 5-8 November 1997, Palo Alto, CA; http://www.zyvex.com/Publications/papers/Foresight97.html.

3004. "Table C4. Wholesale Propane Prices by Region and State, Cents per Gallon, 2003-2004 Heating Season Monthly," Weekly Petroleum Status Report, Energy Information Administration, U.S. Department of Energy, 10 February 2004; http://www.eia.doe.gov/pub/oil_gas/petroleum/data_publications/weekly_petroleum_status_report/current/pdf/tablec4.pdf.

3005. "Cotton and Wool Outlook," CWS-0200, Economic Research Service, U.S. Department of Agriculture, approved by the World Agricultural Outlook Board, 13 March 2000; http://usda.mannlib.cornell.edu/reports/erssor/field/cws-bb/2000/cws0200.pdf.

3006. "Shell Eggs: Weekly Combined Regional Shell Eggs," USDA/AMS Poultry Programs, Market News Branch, Washington, DC, 23 January 2004; http://www.ams.usda.gov/mnreports/wa_py001.txt.

3007. "5 Area Weekly Weighted Average Direct Slaughter Cattle," Livestock, Meat & Wool Weekly Summary and Statistics, week ending 17 January 2004, Vol. 72, No. 03, page 10; http://www.ams.usda.gov/LSMNpubs/pdf_weekly/lmweek.pdf.

3008. Farid Alakbarov, Iskandar Aliyev, "Silk Road: The Origin of the Mulberry Trees," Azerbaijan International, 8(Autumn 2000); http://www.azer.com/aiweb/categories/magazine/83_folder/83_articles/83_silk.html.

3009. "Imports and Exports of Textiles and Garments in Jan-Jul Period 2001 [China]: Table 2. Exports of Textile Raw Materials," TI Weekly, 2001; http://textile.unet.net.cn/imex107.htm.

3010. "Beluga Caviar," Savara Group, Inc., January 2004; http://www.russianfoods.com/showroom/product014C9/_print_/default.asp.

3011. "Akoya Pearl Necklace: 18-inch, 8.5mm AA Akoya Sea Pearl Necklace," Pearls of Joy, January 2004; http://www.pearlsofjoy.com/akoya-8.html.

3012. "Physical and Chemical Properties of Stones: Pearl," Semiprecious.com, 2004; http://www.semiprecious.com/Physical_chemical_properties.htm.

3013. American Type Culture Collection, "ATCC Serum-Free Cell Lines: HeLa/SF [serum free derivative of HeLa (ATCC CCL-2)]," 14 May 1998; http://www.atcc.org/hilights/serum-free.html.

3014. Stephen L. Gillett, "Near-term nanotechnology: The molecular fabrication of nanostructured materials," Nanotechnology 7(September 1996):168-176.

3015. "2003 Lexus SC 430 — Specs," New-Cars.com, 28 January 2004; http://www.new-cars.com/2003/lexus/lexus-sc-430-specs.html.

3016. "Inspiron 8600 Details," Dell Computers, 28 January 2004; http://www1.us.dell.com/content/products/productdetails.aspx/inspn_8600?c=us&cs=19&l=en&s=dhs.

3017. MER Corporation, "Single-Wall Carbon Nanotubes," January 2004; http://www.mercorp.com/mercorp/Nanotubes/Nanotubes.html; Carbon Solutions, Inc., "Carbon nanotubes: price," http://www.carbonsolution.com/products.htm.

3018. "Product Catalog: Carbon Nanotubes," Carbon Nanotechnologies Inc., January 2004; http://www.cnanotech.com/pages/store/6-0_online_store.html.

3019. Gary H. Bernstein, "Microprocessor: VI. Construction of Microprocessors," Microsoft® Encarta® Online Encyclopedia 2004; http://encarta.msn.com/encyclopedia_761559091/microprocessor.html.

3020. Michael Kanellos, "Intel, AMD neck and neck in chip costs," CNET Networks News.com, 16 May 2002; http://news.com.com/2100-1001-914985.html.

3021. G. Binnig, H. Rohrer, "Scanning tunneling microscopy," Helv. Phys. Acta 55(1982):726-735; G. Binnig, H. Rohrer, C. Gerber, E. Weibel, "Surface studies by scanning tunneling microscopy," Phys. Rev. Lett. 49(1982):57-61; G. Binnig, H. Rohrer, C. Gerber, E. Weibel, "Tunneling through a controllable vacuum gap," Appl. Phys. Lett. 40(1982):178-179; Gerd Binnig, Heinrich Rohrer, "The Scanning Tunneling Microscope," Sci. Amer. 253(August 1985):50-56; Gerd Binnig, Heinrich Rohrer, "Scanning tunneling microscopy from birth to adolescence," Rev. Mod. Phys. 59(July 1987):615-625.

3022. J.W. Gadzuk, "STM not developed in a vacuum," Physics Today 40(1987).

3023. R.D. Young, J. Ward, F. Scire, "Observation of metal-vacuum-metal tunneling, field emission, and the transition region," Phys. Rev. Lett. 27(1971):922-924.

3024. R.D. Young, J. Ward, F. Scire, "The Topografiner: an instrument for measuring surface microtopography," Rev. Sci. Instr. 43(1972):999-1011.

3025. David M. Berube, John D. Shipman, Nanohype, Prometheus Press, 2004, in preparation. Also: David M. Berube, personal communications to Robert A. Freitas Jr., 26-27 September 2003.

3026. Howard Lovy, "Clash of the Nanotech Titans," Howard Lovy's Nanobot, 1 November 2003; http://nanobot.blogspot.com/2003_11_30_nanobot_archive.html.

3027. K. Eric Drexler, "Chapter 11. Engines of Destruction," Engines of Creation: The Coming Era of Nanotechnology, Anchor Press/Doubleday, New York, 1986; http://www.foresight.org/EOC/EOC_Chapter_11.html.

3028. Mark Avrum Gubrud, "Nanotechnology and international security," paper presented at the 5th Foresight Conference, November 1997; http://www.foresight.org/Conferences/MNT05/Papers/Gubrud/.

3029. "Dangers of Molecular Manufacturing," Center for Responsible Nanotechnology, 2004; http://crnano.org/dangers.htm.

3030. Lev Navrozov, "Molecular nano weapons: Research in China and talk in the West," NewsMax.com, 27 February 2004; http://www.newsmax.com/archives/articles/2004/2/27/101732.shtml.

3031. Britt D. Gillette, Conquest of Paradise: An End-times Nano-Thriller, Writers Club Press, New York, 2003.

3032. John Robert Marlow, Nano, St. Martin's Press, New York, 2004.

3033. Dan Piraro, "Bizarro," Chronicle Features, San Francisco Chronicle, San Francisco, CA, 10 January 1991. Reprinted in J. Doyne Farmer, Alletta d'A. Belin, "Artificial life: the coming evolution," in C.G. Langton, C. Taylor, J.D. Farmer, S. Rasmussen, eds., Artificial Life II, Volume X of SFI Studies in the Sciences of Complexity, Addison-Wesley, Redwood City, CA, 1992, pp. 815-840, at page 838.

3034. Clive Thompson, "The Virus Underground," The New York Times, 8 February 2004; http://www.nytimes.com/2004/02/08/magazine/08WORMS.html.

3035. Bill Joy, "Act now to keep new technologies out of destructive hands," New Perspectives Quarterly 17(Summer 2000); http://www.pugwash.org/reports/pim/pim18.htm.

3036. James R. Hughes, "Relinquishment or Regulation: Dealing with Apocalyptic Technological Threats," Trinity College, Fall 2001; http://www.changesurfer.com/Acad/RelReg.pdf.

3037. Spencer Reiss, "Hope Is a Lousy Defense," Wired, December 2003; http://www.wired.com/wired/archive/11.12/billjoy_pr.html.

3038. Glenn Harlan Reynolds "Techno Worries Miss the Target," SpeakOut.com, 8 June 2000; http://speakout.com/activism/opinions/5298-1.html.

3039. Garrett Hardin, Nature and Man's Fate, New American Library, New York, 1959, p. 283.

3040. Mae-Wan Ho, "Will Computers Become Super-Human. What's wrong with Eric Drexler's molecular machines?" Institute of Science in Society (ISIS), London, U.K., 2002; http://www.i-sis.org.uk/computersvshumans.php.

3041. R.E. Smalley, "Chemistry on the Nanometer Scale — Introductory Remarks," 1996 Welch Conference in Chemistry; http://cnst.rice.edu/NanoWelch.html.

3042. Robert F. Service, "Is nanotechnology dangerous?" Science 290(24 November 2000):1526-1527.

3043. R. Green, H.F. Noller, "Ribosomes and translation," Annu. Rev. Biochem. 66(1997):679-716; J.H. Cate, M.M. Yusupov, G.Z. Yusupova, T.N. Earnest, H.F. Noller, "X-ray crystal structures of 70S ribosome functional complexes," Science 285(24 September 1999):2095-2104; J.D. Puglisi, S.C. Blanchard, R. Green, "Approaching translation at atomic resolution," Nat. Struct. Biol. 7(October 2000):855-861.

3044. "Voxels Project," http://www.thefirst.org/jefft/voxels/index.html; "Voxels Project — Cubes," http://www.thefirst.org/jefft/voxels/cubes.html; RealVideo animation of Cube assembly, http://www.thefirst.org/jefft/voxels/voxelsLW.ram; "Voxels Project — Spheres," http://www.thefirst.org/jefft/voxels/spheres.html.

3045. Michael Page, Donald W. Brenner, "Hydrogen abstraction from a diamond surface: Ab initio quantum chemical study using constrained isobutane as a model," J. Am. Chem. Soc. 113(1991):3270-3274; "Ab initio quantum chemical study of hydrogen abstraction from isobutane constrained to model a diamond surface," in Russell Messier, Jeffrey T. Glass, James E. Butler, Rustum Roy, eds., Proceedings of the Second International Conference, New Diamond Science and Technology, Materials Research Society, Pittsburgh, PA, 1991, pp. 45-50.

3046. Susan B. Sinnott, Richard J. Colton, Carter T. White, Donald W. Brenner, "Surface patterning by atomically-controlled chemical forces: molecular dynamics simulations," Surf. Sci. 316(1994):L1055-L1060.

3047. D.W. Brenner, S.B. Sinnott, J.A. Harrison, O.A. Shenderova, "Simulated engineering of nanostructures," Nanotechnology 7(1996):161-167; http://www.zyvex.com/nanotech/nano4/brennerPaper.pdf.

3048. Fedor N. Dzegilenko, Deepak Srivastava, Subhash Saini, "Simulations of carbon nanotube tip assisted mechano-chemical reactions on a diamond surface," Nanotechnology 9(December 1998):325-330; http://www.nanology.ustc.edu.cn/chinese/.%5Cpdf%5Cna8404.pdf.

3049. K. Eric Drexler, "Nanomachinery: Atomically precise gears and bearings," IEEE Micro Robots and Teleoperators Workshop, Hyannis, Cape Cod, November 1987.

3050. Ralph C. Merkle, "A Proof About Molecular Bearings," Nanotechnology 4(1993):86-90; http://www.zyvex.com/nanotech/bearingProof.html.

3051. J.W. Lyding, K. Hess, G.C. Abeln, D.S. Thompson, J.S. Moore, M.C. Hersam, E.T. Foley, J. Lee, Z. Chen, S.T. Hwang, H. Choi, P.H. Avouris, I.C. Kizilyalli, "UHV-STM nanofabrication and hydrogen/deuterium desorption from silicon surfaces: implications for CMOS technology," Appl. Surf. Sci. 130(1998):221-230.

3052. E.T. Foley, A.F. Kam, J.W. Lyding, P.H. Avouris, P. H. (1998), "Cryogenic UHV-STM study of hydrogen and deuterium desorption from Si(100)," Phys. Rev. Lett. 80(1998):1336-1339.

3053. M.C. Hersam, G.C. Abeln, J.W. Lyding, "An approach for efficiently locating and electrically contacting nanostructures fabricated via UHV-STM lithography on Si(100)," Microelectronic Engineering 47(June 1999):235-237.

3054. Wilson Ho, Hyojune Lee, "Single bond formation and characterization with a scanning tunneling microscope," Science 286(26 November 1999):1719-1722; http://www.physics.uci.edu/~wilsonho/stm-iets.html.

3055. L.J. Lauhon, W. Ho, "Inducing and observing the abstraction of a single hydrogen atom in bimolecular reaction with a scanning tunneling microscope," J. Phys. Chem. 105(2000):3987-3992.

3056. Robert L. Park, "Tiny Terrors," New Scientist (5 July 2003):22.

3057. Noriaki Oyabu, Oscar Custance, Insook Yi, Yasuhiro Sugawara, Seizo Morita, "Mechanical vertical manipulation of selected single atoms by soft nanoindentation using near contact atomic force microscopy," Phys. Rev. Lett. 90(2 May 2003):176102; http://link.aps.org/abstract/PRL/v90/e176102.

3058. Robert H. Goddard, "A Method of Reaching Extreme Altitudes," Smithsonian Miscellaneous Collections, Vol. 71, Number 2, The Smithsonian Institution, City of Washington, 1919.

3059. R.A. Smith et al, "BIS lunar spaceship," J. Brit. Interplanet. Soc., 1939; H.E. Ross et al, J. Brit. Interplanet. Soc., 1949; http://www.geocities.com/CapeCanaveral/Launchpad/6133/moonlanding.html.

3060. Henry Prevost Babbage, Babbage's Calculating Engines, Charles Babbage Institute Reprint Series for the History of Computing, Volume 2, Tomash Publishers, Los Angeles, CA, 1982. Originally published in 1889.

3061. Anthony Hyman, Charles Babbage: Pioneer of the Computer, Oxford University Press, Oxford, 1982.

3062. Stan Augarten, Bit by Bit: An Illustrated History of Computers, Ticknor and Fields, New York, 1984.

3063. H.W. Buxton, Memoirs of the Life and Labours of the Late Charles Babbage, Esq., F.R.S., Anthoy Hyman, ed., Tomash Publishers, Los Angeles, 1988.

3064. Doron Swade, Charles Babbage and his Calculating Engines, Science Museum, London, 1991.

3065. Doron D. Swade, "Redeeming Charles Babbage's mechanical computer," Sci. Amer. 268(February 1993):86-91.

3066. John Walker, "The Analytical Engine," 2004; http://www.fourmilab.ch/babbage/contents.html.

3067. Report of the Committee, consisting of Professor Cayley, Dr. Farr, Mr. J. W. L. Glaisher, Dr. Pole, Professor Fuller, Professor A. B. W. Kennedy, Professor Clifford, and Mr. C. W. Merrifield, appointed to consider the advisability and to estimate the expense of constructing Mr. Babbage's Analytical Machine, and of printing Tables by its means. Drawn up by Mr. Merrifield. 1878; http://www.fourmilab.ch/babbage/baas.html.

3068. Lewis Coe, The Telegraph: A History of Morse's Invention and Its Predecessors in the United States, McFarland & Company, 1993; Tom Standage, The Victorian Internet: The Remarkable Story of the Telegraph and the Nineteenth Century's On-Line Pioneers, Berkley Publishing Group, 1999; Anita Louise McCormick, The Invention of the Telegraph and Telephone in American History, Enslow Publishers, Inc., 2003.

3069. Raymond Kurzweil, The Age of Intelligent Machines, MIT Press, Cambridge MA, 1990.

3070. Joel Shurkin, Engines of the Mind: A History of the Computer, W.W. Norton and Company, New York, 1984, p. 104.

3071. William Gibson, Bruce Sterling, The Difference Engine, Gollancz, London, 1990 and Bantam Books, New York, 1991.

3072. Eugenii Katz, "Giovanni Caselli," Hebrew University of Jerusalem, 2003; http://chem.ch.huji.ac.il/~eugeniik/history/caselli.html.

3073. Lawrence Lessig, The Future of Ideas: The Fate of the Commons in a Connected World, Random House, New York, 2001.

3074. Mark A. Reed, James M. Tour, "Computing with molecules," Sci. Amer. 282(June 2000):86-93.

3075. Philip G. Collins, Phaedon Avouris, "Nanotubes for electronics," Sci. Amer. 283(December 2000):62-69.

3076. Philip G. Collins, Michael S. Arnold, Phaedon Avouris, "Engineering carbon nanotubes and nanotube circuits using electrical breakdown," Science 292(27 April 2001):706-709.

3077. F. Nakajima, Y. Miyoshi, J. Motohisa, T. Fukui, "Single-electron AND/NAND logic circuits based on a self-organized dot network," Appl. Phys. Lett. 83(2003):2680.

3078. C.P. Husband, S.M. Husband, J.S. Daniels, J.M. Tour, "Logic and memory with Nanocell circuits," IEEE Trans. Electron Devices 50(2003):1865-1975.

3079. R.W. Keyes, "Miniaturization of electronics and its limits," IBM Journal of Research and Development 32(January 1988).

3080. B.C. Crandall, ed., Nanotechnology: Molecular Speculations on Global Abundance, MIT Press, Cambridge MA, 1996.

3081. "Topics of the Times: A Severe Strain on Credibility," The New York Times, 13 January 1920, p. 12; "A Correction," The New York Times, 17 July 1969, p. 43; http://it.is.rice.edu/~rickr/goddard.editorial.html.

3082. J.K. Gimzewski, C. Joachim, R.R. Schlittler, V. Langlais, H. Tang, I. Johannsen, "Rotation of a Single Molecule Within a Supramolecular Bearing," Science 281(24 July 1998):531-533.

3083. John Cumings, A. Zettl, "Low-friction nanoscale linear bearing realized from multiwall carbon nanotubes," Science 289(28 July 2000):602-604.

3084. D.M. Eigler, E.K. Schweizer, "Positioning Single Atoms with a Scanning Tunneling Microscope," Nature 344(1990):524-526.

3085. Paul E. Sheehan, Charles M. Lieber, "Nanotribology and Nanofabrication of MoO_3 Structures by Atomic Force Microscopy," Science 272(24 May 1996):1158-1161.

3086. M.T. Cuberes, R.B. Schlittler, James K. Gimzewski, "Room-temperature repositioning of individual C_{60} molecules at Cu steps: Operation of a molecular counting device," Appl. Phys. Lett. 69(11 November 1996):3016-3018.

3087. T.R. Ramachandran, C. Baur, A. Bugacov, A. Madhukar, B.E. Koel, A. Requicha, C. Gazen, "Direct and controlled manipulation of nanometer-sized particles using the non-contact atomic force microscope," Nanotechnology 9(September 1998):237-245; C. Baur, A. Bugacov, B.E. Koel, A. Madhukar, N. Montoya, T.R. Ramachandran, A.A.G. Requicha, R. Resch, P. Will, "Nanoparticle manipulation by mechanical pushing, underlying phenomena and real-time monitoring," Nanotechnology 9(December 1998):360-364; R. Resch, C. Baur, A. Bugacov, B.E. Koel, A. Madhukar, A. Requicha, P. Will, "Building and manipulating 3-D and linked 2-D structures of nanoparticles using scanning force microscopy," 9 March 1998, Laboratory for Molecular Robotics; http://alicudi.usc.edu:80/~lmr.

3088. MinFeng Yu, Mark J. Dyer, George D. Skidmore, Henry W. Rohrs, XueKun Lu, Kevin D. Ausman, James R. Von Ehr, Rodney S. Ruoff, "Three dimensional manipulation of carbon nanotubes under a scanning electron microscope," Nanotechnology 10(September 1999):244-252; http://www.foresight.org/Conferences/MNT6/Papers/Yu/index.html.

3089. R.E. Smalley, personal communication to Ralph C. Merkle, 1997.

3090. V. Ryan, "The stone arch bridge," 2001; http://www.technologypupil.com/struct1/arch1.htm. See also: John Page, Masonry Arch Bridges, The Stationery Office, 1994 (ISBN 0115511903); Ira Osborn Baker, A Treatise on Masonry Construction, Ninth Edition, 1899.

3091. Design for Assembly, Penton Education Division, 1990 (ISBN 9990228582).

3092. Alan Redford, Jan Chal, Design for Assembly: Principles and Practice, McGraw-Hill, New York, 1994.

3093. Hubert K. Rampersad, Integrated and Simultaneous Design for Robotic Assembly, John Wiley & Sons, New York, 1995.

3094. Samir B. Billatos, Nadia A. Basaly, eds., Design for Manufacturing and Assembly, American Society of Mechanical Engineers, 1996.

3095. O. Molloy, S. Tilley, E.A. Warman, Design for Manufacturing and Assembly — Concepts, Architectures and Implementation, Kluwer Academic Publishers, New York, 1998.

3096. James G. Bralla, ed., Design for Manufacturability Handbook, Second Edition, McGraw-Hill Professional, New York, 1998.

3097. Joe Greco, "Design for Manufacturability and Assembly," Internet Business Systems, Inc., 2001; http://www.mcadcafe.com/MCADVision/feature/Design.html.

3098. Peter Dewhurst, Winston Knight, Geoffrey Boothroyd, Product Design for Manufacture & Assembly, Second Edition, Marcel Dekker, New York, 2001.

3099. Luiz S. Homem De Mello, Sukhan Lee, eds., Computer-Aided Mechanical Assembly Planning, Kluwer Academic Publishers, 1991.

3100. A. Delchambre, Computer-Aided Assembly Planning, Chapman and Hall, 1992.

3101. Elisha Sacks, Leo Joskowicz, Ralph Schultheiss, Min-Ho Kyung, "Robust kinematic synthesis of mechanical systems with the configuration space method," Technical Report of the Leibniz Center, May 2002; http://leibniz.cs.huji.ac.il/tr/acc/2002/HUJI-CSE-LTR-2002-24_musme2002.pdf. See also: Min-Ho Kyung, "Computer-Aided Kinematic Synthesis of Mechanical Systems Using Configuration Space," Ph.D. Dissertation, Department of Computer Science, Purdue University, August 2001.

3102. M. Nelson, C. Shipbaugh, "The Potential of Nanotechnology for Molecular Manufacturing," Document No. MR-615-RC, RAND Corp., Santa Monica, CA, 1995; http://www.rand.org/publications/MR/MR615/.

3103. Neil Jacobstein, Ralph Merkle, Robert Freitas, "Balancing the National Nanotechnology Initiative's R&D Portfolio: A Foresight/IMM White Paper submitted to the White House Office of Science and Technology Policy, 29 May 2002," Foresight Update, No. 52, 31 August 2003, pp. 1, 14-15; http://www.foresight.org/Updates/Update52/Update52.1.html#BalancingNNI or http://www.foresight.org/impact/NNI_White_paper.pdf.

3104. Ralph C. Merkle, "Focusing on Assemblers," Foresight Update, No. 51, 15 April 2003, p. 2.

3105. "System Engineering Definitions," Centre for Systems Engineering, University College London (UCLse); http://www.ucl.ac.uk/syseng/pages/sedef.html.

3106. Chris Phoenix, Eric Drexler, "Safe exponential manufacturing," Nanotechnology 15(2004):869-872; http://www.iop.org/EJ/news/-topic=763/journal/0957-4484. See also: Paul Rincon, "Nanotech guru turns back on 'goo'," BBC News Online UK Edition, 9 June 2004; http://news.bbc.co.uk/1/hi/sci/tech/3788673.stm; and Liz Kalaugher, "Drexler dubs 'grey goo' fears obsolete," Nanotechweb.org, 9 June 2004; http://www.nanotechweb.org/articles/society/3/6/1/1.

3107. Ronald Kotulak, "Science on verge of new 'Creation': Labs say they have nearly all the tools to make artificial life," Sun-Sentinel Tribune, 28 March 2004; http://www.sun-sentinel.com/news/local/southflorida/chi-0403280359mar28,0,4395528.story?coll=sfla-home-headlines.

3108. Programmable Artificial Cell Evolution (PACE) project; http://wills.gex.gmd.de/bmcmyp/Data/PACE/Public.

3109. ProtoLife; http://www.protolife.net.

3110. Ludwig Maximilians University, paper to appear in Angew. Chem. Intl. Ed. (2004); "DNA has Nano Building in Hand," Technology Research News, 24 March 2004; http://www.technologyreview.com/articles/rnb_032404.asp.

3111. W. Wayt Gibbs, "Synthetic Life," 26 April 2004; http://www.sciam.com/print_version.cfm?articleID=0009FCA4-1A8F-1085-94F483414B7F0000.

3112. Charles Babbage, Passages from the Life of a Philosopher, Longman, Green, Longman, Roberts and Green, London, 1864. Excerpted in Harper's New Monthly Magazine, December 1864, pp. 34-39; http://web.archive.org/web/20021106030600/http://www.hexatron.com/Bab/; reprinted as Charles Babbage, Passages from the Life of a Philosopher, Dawsons of Pall Mall, London, 1968; and in Martin Campbell-Kelly, ed., Charles Babbage: Passages from the Life of a Philosopher, Rutgers University Press and IEEE Press, Piscataway, NJ, 1994.

3113. Jurgen Altmann, "Military uses of nanotechnology: Perspectives and concerns," Security Dialogue 35(March 2004):61-79.

3114. Rüdiger Haum, Ulrich Petschow, Michael Steinfeldt, Arnim von Gleich, Nanotechnology and Regulation within the Framework of the Precautionary Principle, Schriftenreihe des IÖW 173/04, Berlin, May 2004. (ISBN 3-932092-74-0); http://www.ioew.de/forschungsfelder/publikationen_template.php?id=4392.

3115. Nicholas Thompson, "Downsizing. Nanotechnology — Why you should sweat the small stuff," The Washington Monthly, October 2000; http://www.washingtonmonthly.com/features/2000/0010.thompson.html.

3116. David R. Lide, Henry V. Kehiaian, CRC Handbook of Thermophysical and Thermochemical Data, CRC Press, Boca Raton, FL, 1994.

3117. James C.F. Wang, George S. Springer, "Vibrational relaxation times in some hydrocarbons in the range 300-900°K," J. Chem. Phys. 59(15 December 1973):6556-6562.

3118. Dwight E. Gray, ed., American Institute of Physics Handbook, Third Edition, McGraw-Hill Book Company, New York, 1972.

3119. T.S. Khasanshin, A.P. Shchemelev, "Sound velocity in liquid n-alkanes," High Temp. 39(2001):60-67.

3120. http://www.e-cats.com/databook/Page%2022.htm.

3121. Marek Pyda, "n-Octane, Crystalline Heat Capacity Data," prediction scheme result on heat capacities of macromolecules, Advanced Thermal Analysis Laboratory, University of Tennessee at Knoxville and Oak Ridge National Laboratory, 25 December 1997; http://web.utk.edu/~athas/databank/paraffin/c8/c8expc.html or http://funnelweb.utcc.utk.edu/~athas/databank/paraffin/c8/c8expc.html.

3122. Ville Kaajakari, Abhijit, Amit Lal, "A frequency addressable ultrasonic microfluidic actuator array," 11th Intl. Conf. on Solid-State Sensors and Actuators (Transducers '01 and Eurosensors XV), 10-14 June 2001; http://www.cae.wisc.edu/~sonicmem/research/actuation/transducers01_web.pdf.

3123. Ninad Shinde, Rashid Bashir, Eckhard Groll, George Chiu, "Design, fabrication, and heat flow analysis of a mesoscopic pulse tube for integrated micro-refrigeration systems," 2000 International Mechanical Engineering Congress and Exposition, American Society of Mechanical Engineers, November 5th –10th, 2000, Orlando, Florida; http://www.ece.purdue.edu/~bashir/projects/micro_refrigeration.html.

3124. Peter Laitenberger, David Pooley, Andrew Stimpson, "Micro electromechanical systems: the reality," The Generics Group Ltd, 2002; http://www.genericsgroup.com/what/consultancy/mems_wp.pdf.

3125. "Capacitive Pressure Sensor Process," Zavracky Group, Microfabrication Laboratory at Northeastern University; http://www.ece.neu.edu/edsnu/zavracky/mfl/programs/soi/soi.html.

3126. Don C. Abeysinghe, Samhita Dasgupta, Joseph T. Boyd, Howard E. Jackson, “A novel MEMS pressure sensor integrated with an optical fiber,” Paper A7.002, Session A7: MEMS, Nano-scale Physics Applications, American Physical Society March Meeting 2001, Seattle, WA, Bulletin of the American Physical Society, Vol. 46, No. 1, 2001; http://www.eps.org/aps/meet/MAR01/baps/abs/S70002.html (abstract).
3127. Ville Kaajakari, Amit Lal, “Pulsed ultrasonic release and assembly of micromachines,” 10th Intl. Conf. on Solid-State Sensors and Actuators, 1999, pp. 212-215.
3128. P.A. Dayton, J.E. Chomas, A.F. Lum, J.S. Allen, J.R. Lindner, S.I. Simon, K.W. Ferrara, “Optical and acoustical dynamics of microbubble contrast agents inside neutrophils,” Biophys. J. 80(March 2001):1547-1556; http://www.biophysj.org/cgi/content/full/80/3/1547.
3129. M.A. Shammari, D.J. Watmough, C.L. Kerr, D.W. Gregory, D.N. Wheatley, “Combined effects of hyperthermia (to 45 degrees C) and ultrasound irradiation on the surface ultrastructure of HeLa cells,” Int. J. Hyperthermia 6(May-June 1990):571-580.
3130. E.C. Unger, T.P. McCreery, R.H. Sweitzer, V.E. Caldwell, Y. Wu, “Acoustically active lipospheres containing paclitaxel: a new therapeutic ultrasound contrast agent,” Invest. Radiol. 33(December 1998):886-892.
3131. D. L. Miller, W. L. Nyborg, “Theoretical investigation of the response of gas-filled micropores and cavitation nuclei to ultrasound,” J. Acoust. Soc. Am. 73(May 1983):1537-1544.
3132. D.L. Miller, E.A. Neppiras, “On the oscillation mode of gas-filled micropores,” J. Acoust. Soc. Am. 77(March 1985):946-953.
3133. D.L. Miller, “Frequency relationships for ultrasonic activation of free microbubbles, encapsulated microbubbles, and gas-filled micropores,” J. Acoust. Soc. Am. 104(October 1998):2498-2505.
3134. S.A. Chesnokov, V.A. Nalimova, A.G. Rinzler, R.E. Smalley, J.E. Fischer, “Mechanical energy storage in carbon nanotube springs,” Phys. Rev. Lett. 82(1999):343-346.
3135. Phillip F. Schewe, Ben Stein, and James Riordon, “Physics News Update,” The American Institute of Physics Bulletin of Physics News 531, 22 March 2001; http://newton.ex.ac.uk/aip/physnews.531.html.
3136. J. Li, C. Papadopoulos, J.M. Xu., “Highly-ordered carbon nanotube arrays for electronics applications,” Appl. Phys. Lett. 75(19 July 1999):367.
3137. Flavio Noca, Michael Hoenk, Brian Hunt, Petros Koumoutsakos, Jens Walther, Thomas Werder, “Bio-inspired acoustic sensors based on artificial stereocilia,” Acoustical Society of America meeting, 5 December 2000, Newport Beach; http://asa.aip.org/web2/asa/abstracts/search.dec00/asa183.html.
3138. Alan Hall, “The sound of one cell growing,” Business Week Online, 2 January 2001; http://www.businessweek.com/bwdaily/dnflash/jan2001/nf2001012_818.htm.
3139. P.A. Tesner, T.D. Snegireva, L.M. Borodina, “Explosive decomposition of acetylene at atmospheric pressure,” Fizika Goreniya I Vzryva 9(January-February 1973):111-115.
3140. Julius A. Nieuwland, Richard R. Vogt, The Chemistry of Acetylene, Reinhold Publ. Co., New York, 1945.
3141. Thomas F. Rutledge, Acetylenic Compounds: Preparation and Substitution Reactions, Reinhold Book Corp., New York, 1968.
3142. M.F. Shostakovskii, A.V. Bogdanova, The Chemistry of Diacetylenes, Wiley, New York, 1974.
3143. H.J. Cantow, ed., Polydiacetylenes, Springer, Berlin, 1984; R.R. Chance, ed., Polydiacetylenes, Martinus Nijhoff, Dordrecht, 1985.
3144. H. Shirakawa, T. Ito, S. Ikeda, Polym. J. 4(1973):460; T.S. Liang, K. Akagi, H. Shirakawa, “Synthesis of polyacetylene ultra-thin film,” Synth. Metals 101(1999):67-68.
3145. A.N. Oraevskii, V.P. Pimenov, A.A. Stepanov, V.A. Shcheglov, “Laser polymerization in gases,” Sov. J. Quant. Electron. 4(November 1974):711-712.
3146. K. Aoki, S. Usuba, M. Yoshida, Y. Kakudate, K. Tanaka, S. Fujiwara, “Raman study of the solid-state polymerization of acetylene at high pressure,” J. Chem. Phys. 89(1 July 1988):529-534.
3147. Mami Sakashita, Hiroshi Yamawaki, Katsutoshi Aoki, “FT-IR study of the solid state polymerization of acetylene under pressure,” J. Phys. Chem. 100(1996):9943-9947.
3148. M. Bernasconi, G.L. Chiarotti, P. Focher, M. Parrinello, E. Tosatti, “Solid-state polymerization of acetylene under pressure: ab initio simulation,” Phys. Rev. Lett. 78(10 March 1997):2008-2011.
3149. Matteo Ceppatelli, Mario Santoro, Roberto Bini, Vincenzo Schettino, “Fourier transform infrared study of the pressure and laser induced polymerization of solid acetylene,” J. Chem. Phys. 113(8 October 2000):5991-6000.
3150. Edwin J. Hart, Christian-Herbert Fischer, Arnim Henglein, “Pyrolysis of acetylene in sonolytic cavitation bubbles in aqueous solution,” J. Phys. Chem. 94(1990):284-290.
3151. Kenneth S. Suslick, John J. Gawlenowski, Paul F. Schubert, Hau H. Wang, “Alkane sonochemistry,” J. Phys. Chem. 87(1983):2299-2301; Ultrasonics 23(January 1984)33-36.
3152. Kenneth S. Suslick, Edward B. Flint, “Sonoluminescence from non-aqueous liquids,” Nature 330(10 December 1987):553-555.
3153. A.A. Atchley, L.A. Crum, in K.S. Suslick, ed., Ultrasound, Its Chemical, Physical, and Biological Effects, VCH Publishers, New York, 1988, p. 1.
3154. S.M. Reddy, J.P. Jones, T.J. Lewis, “The coexistence of pressure waves in the operation of quartz-crystal shear-wave sensors,” J. Appl. Phys. 83(1 March 1998):2524-2532.
3155. Michelle L. Gee, Patricia M. McGuiggan, Jacob N. Israelachvili, “Liquid to solidlike transitions of molecularly thin films under shear,” J. Chem. Phys. 93(1 August 1990):1895-1906.
3156. R.P. Benedict, Fundamentals of Pipe Flow, John Wiley and Sons, New York, 1980.
3157. Y.C. Fung, Biodynamics: Circulation, Springer-Verlag, New York, 1984.
3158. Osborne Reynolds, “An experimental investigation of the circumstances which determine whether the motion of water shall be direct or sinuous, and of the law of resistance in parallel channels,” Phil. Trans. Roy. Soc. 174(1883):935-982.
3159. Edward M. Purcell, “Life at low Reynolds number,” Amer. J. Phys. 45(1977):3-11; http://brodylab.eng.uci.edu/~jpbrody/reynolds/lowpurcell.html.
3160. George M. Whitesides, Abraham D. Stroock, “Fluid mechanics in microchannels,” Physics Today 54(June 2001):42-; http://www.physicstoday.com/pt/vol-54/iss-6/captions/p42box2.html.
3161. Robert C. Weast, Handbook of Chemistry and Physics, 49th Edition, CRC, Cleveland OH, 1968.
3162. Robert H. Austin, James P. Brody, R. Goldstein, Paul Yager, “Biotechnology at low Reynolds numbers,” Biophys. J. (December 1996); http://publish.aps.org/eprint/gateway/epget/aps1996jul26_001/main.pdf.
3163. G.K. Batchelor, An Introduction to Fluid Dynamics, Cambridge University Press, 1967.
3164. Jean-Louis Barrat, Lyderic Bocquet, “Hydrodynamic boundary conditions and correlation functions of confined fluids,” Phys. Rev. Lett. 70(1993):2726-2729.
3165. Martin Schnorf, Ingo Potrykus, Gunther Neuhaus, “Microinjection technique: Routine system for characterization of microcapillaries by bubble pressure measurement,” Experimental Cell Research 210(1994):260-267.
3166. Robert E. Tuzun, Donald W. Noid, Bobby G. Sumpter, Ralph C. Merkle, “Dynamics of fluid flow inside carbon nanotubes,” Nanotechnology 7(1996):241-246.
3167. Robert E. Tuzun, Donald W. Noid, Bobby G. Sumpter, Ralph C. Merkle, “Dynamics of He/C_{60} flow inside carbon nanotubes,” Nanotechnology 8(1997):112-118.
3168. R.D. Groot, N.M. Faber, J.P. van der Eerden, “Hard sphere fluids near a hard wall and a hard cylinder,” Molec. Phys. 62(November 1987):861-874.
3169. Jee-Ching Wang, Kristen A. Fichthorn, “Effects of chain branching on the structure of interfacial films of decane isomers,” J. Chem. Phys. 108(22 January 1998):1653-1663.
3170. Paz Padilla, Soren Toxvaerd, “Fluid alkanes in confined geometries,” J. Chem. Phys. 101(15 July 1994):1490-1502.
3171. S. Toxvaerd, “Molecular dynamics calculation of the equation of state of alkanes,” J. Chem. Phys. 93(15 September 1990):4290-4295.
3172. P. Padilla, S. Toxvaerd, “Self-diffusion in n-alkane fluid models,” J. Chem. Phys. 94(15 April 1991):5650-5654.
3173. S. Gupta, D.C. Koopman, G.B. Westermann-Clark, I.A. Bitsanis, “Segmental dynamics and relaxation of n-octane at solid-liquid interfaces,” J. Chem. Phys. 100(1 June 1994):8444-8453.
3174. S.T. Cui, P.T. Cummings, H.D. Cochran, “Molecular dynamics simulation of the rheological and dynamical properties of a model alkane fluid under confinement,” J. Chem. Phys. 111(15 July 1999):1273-1280.
3175. T.K. Xia, Jian Quyang, M.W. Ribarsky, U. Landman, “Interfacial alkane films,” Phys. Rev. Lett. 69(28 September 1992):1967-1970.
3176. D.C. Koopman, S. Gupta, R.K. Ballamudi, G.B. Westermann-Clark, I.A. Bitsanis, “Structural patterns and molecular mobility inside the interface between an fcc solid and liquid n-octane,” Chem. Eng. Sci. 49(1994):2907-2920.

3177. P. Smith, R.M. Lynden-Bell, J.C. Earnshaw, W. Smith, “The surface ordered phase of liquid heptadecane: a simulation study,” Molec. Phys. 96(January 1999):249-257.

3178. Marjolein Dijkstra, “Confined thin films of linear and branched alkanes,” J. Chem. Phys. 107(22 August 1997):3277-3288.

3179. R.K. Ballamudi, I.A. Bitsanis, “Energetically driven liquid-solid transitions in molecularly thin n-octane films,” J. Chem. Phys. 105(1 November 1996):7774-7782.

3180. Yantse Wang, Kirk Hill, Jonathan G. Harris, “Confined thin films of a linear and branched octane. A comparison of the structure and solvation forces using molecular dynamics simulations,” J. Chem. Phys. 100(15 February 1994):3276-3285.

3181. Yantse Wang, Kirk Hill, Jonathan Harris, “Thin films of n-octane confined between parallel solid surfaces. Structure and adhesive forces vs. film thickness from molecular dynamics simulations,” J. Phys. Chem. 97(2 September 1993):9013-9021.

3182. Yantse Wang, Kirk Hill, Jonathan Harris, “Comparison of branched and linear octanes in the surface force apparatus. A molecular dynamics study,” Langmuir 9(August 1993):1983-1985.

3183. I.K. Snook, W. van Megan, “Solvation forces in simple dense fluids,” J. Chem. Phys. 72(1 March 1980):2907-2913.

3184. M. Schoen, D.J. Diestler, J.H. Cushman, “Fluids in micropores. I. Structure of a simple classical fluid in a slit pore,” J. Chem. Phys. 87(1 November 1987):5464-5476.

3185. Jianping Gao, W.D. Luedtke, Uzi Landman, “Structure and solvation forces in confined films: linear and branched alkanes,” J. Chem. Phys. 106(8 March 1997):4309-4318.

3186. C.L. Rhykerd, Jr., M. Schoen, D.J. Diestler, J.H. Cushman, “Epitaxy in simple classical fluids in micropores and near-solid surfaces,” Nature 330(3 December 1987):461-463.

3187. Ryan Y. Jin, Kihyung Song, William L. Hase, “Molecular dynamics simulations of the structures of alkane/hydroxylated α-Al_2O_3(0001) interfaces,” J. Phys. Chem. 104(2000):2692-2701.

3188. Bogdan Bilinski, “Free surface energy changes in graphite/n-hexadecane system,” Mater. Chem. Phys. 18(November 1987):231-244.

3189. H.-C. Chang, J.-C. Lin, “Structure and bonding of C_2H_2 on diamond C(111)-1x1:H: Infrared spectroscopy and exciton calculations,” J. Phys. Chem. 100(1996):7018-7025.

3190. R.G. Horn, J.N. Israelachvili, “Direct measurement of structural forces between two surfaces in a nonpolar liquid,” J. Chem. Phys. 75(1 August 1981):1400-1411.

3191. S.J. O’Shea, M.E. Welland, T. Rayment, “Solvation forces near a graphite surface measured with an atomic force microscope,” Appl. Phys. Lett. 60(11 May 1992):2356-2358.

3192. H.K. Christenson, R.G. Horn, J.N. Israelachvili, “Measurement of forces due to structure in hydrocarbon liquids,” J. Colloid. Interface Sci. 88(July 1982):79-88.

3193. Hugo K. Christenson, “Experimental measurements of solvation forces in nonpolar liquids,” J. Chem. Phys. 78(1 June 1983):6906-6913.

3194. H.K. Christenson, D.W.R. Gruen, R.G. Horn, J.N. Israelachvili, “Structuring in liquid alkanes between solid surfaces: Force measurements and mean-field theory,” J. Chem. Phys. 87(1 August 1987):1834-1841.

3195. Jacob N. Israelachvili, Stephen J. Kott, Michelle L. Gee, Thomas A. Witten, “Forces between mica surfaces across hydrocarbon liquids: Effects of branching and polydispersity,” Macromolecules 22(1989):4247-4253.

3196. Michelle L. Gee, Jacob N. Israelachvili, “Interactions of surfactant monolayers across hydrocarbon liquids,” J. Chem. Soc. Faraday Trans. 86(1990):4049-4058.

3197. John Peanasky, Lenore L. Cai, Steve Granick, Carl R. Kessel, “Nanorheology of confined polymer melts. 3. Weakly adsorbing surfaces,” Langmuir 10(1994):3874-3879.

3198. R.G. Horn, J.N. Israelachivili, E. Perez, “Forces due to structure in a thin liquid crystal film,” J. Phys. 42(January 1981):39-52.

3199. Jacob N. Israelachvili, Stephen J. Kott, Michelle L. Gee, Thomas A. Witten, “Entropic orientational forces between surfaces in anisotropic liquids,” Langmuir 5(1989):1111-1113.

3200. Steve Granick, A. Levent Demirel, Lenore L. Cai, John Peanasky, “Soft matter in a tight spot: Nanorheology of confined liquids and block copolymers,” Isr. J. Chem. 35(1995):75-84.

3201. Soren Toxvaerd, “The structure and thermodynamics of a solid-fluid interface,” J. Chem. Phys. 74(1 February 1981):1998-2005.

3202. J.J. Magda, M. Tirrell, H.T. Davis, “Molecular dynamics of narrow, liquid-filled pores,” J. Chem. Phys. 83(15 August 1985):1888-1901.

3203. Jacob Klein, Eugenia Kumacheva, “Simple liquids confined to molecularly thin layers: I. Confinement-induced liquid-to-solid phase transitions,” J. Chem. Phys. 108(22 April 1998):6996-7009.

3204. M. Schoen, J.H. Cushman, D.J. Diestler, C.L. Rhykerd, Jr., “Fluids in micropores. II. Self-diffusion in a simple classical fluid in a slit pore,” J. Chem. Phys. 88(15 January 1988):1394-1406.

3205. P.A. Thompson, G.S. Grest, M.O. Robbins, “Phase transitions and universal dynamics in confined films,” Phys. Rev. Lett. 68(1992):3448-3451.

3206. Mark O. Robbins, Peter A. Thompson, Gary S. Grest, “Simulations of nanometer-thick lubricating films,” Mater. Res. Bull. 18(May 1993):45-49.

3207. Jianping Gao, W.D. Luedtke, Uzi Landman, “Layering transitions and dynamics of confined liquid films,” Phys. Rev. Lett. 79(28 July 1997):705-708.

3208. Jacob N. Israelachvili, “Measurement of the viscosity of liquids in very thin films,” J. Colloid. Interface Sci. 110(March 1986):263-271.

3209. Jacob N. Israelachvili, Stephen J. Kott, “Shear properties and structure of simple liquids in molecularly thin films: The transition from bulk (continuum) to molecular behavior with decreasing film thickness,” J. Colloid. Interface Sci. 129(May 1989):461-467.

3210. D.Y.C. Chan, R.G. Horn, “The drainage of thin liquid films between solid surfaces,” J. Chem. Phys. 83(15 November 1985):5311-5324.

3211. J.N. Israelachvili, “Measurements of the viscosity of thin fluid films between two surfaces with and without adsorbed polymers,” Colloid. Polym. Sci. 264(December 1986):1060-1065.

3212. R.G. Horn, D.T. Smith, W. Haller, “Surface forces and viscosity of water measured between silica sheets,” Chem. Phys. Lett. 162(20 October 1989):404-408.

3213. Jacob Klein, Yoichiro Kamiyama, Hisae Yoshizawa, Jacob N. Israelachvili, Glenn H. Fredrickson, Philip Pincus, Lewis J. Fetters, “Lubrication forces between surfaces bearing polymer brushes,” Macromolecules 26(1993):5552-5560.

3214. S.A. Gupta, H.D. Cochran, P.T. Cummings, “Shear behavior of squalene and tetracosane under extreme confinement. III. Effect of confinement on viscosity,” J. Chem. Phys. 107(15 December 1997):10335-10343.

3215. S.A. Gupta, H.D. Cochran, P.T. Cummings, “Shear behavior of squalene and tetracosane under extreme confinement. I. Model, simulation method, and interfacial slip,” J. Chem. Phys. 107(15 December 1997):10316-10325.

3216. Sundaram Balasubramanian, Michael L. Klein, J. Ilja Siepmann, “Monte Carlo investigations of hexadecane films on a metal substrate,” J. Chem. Phys. 103(22 August 1995):3184-3195.

3217. T.K. Xia, Uzi Landman, “Molecular dynamics of adsorption and segregation from an alkane mixture,” Science 261(3 September 1993):1310-1312.

3218. V.D. Gupta, U. Kapur, C. Mehrotra, “A random-walk model for hydrocarbon-type chains with short-range correlations,” J. Phys. A 2(July 1969):442-447.

3219. S.J. Cyvin, Jianji Wang, J. Brunvoll, Shiming Cao, Ying Li, B.N. Cyvin, Yugang Wang, “Staggered conformers of alkanes: complete solution of the enumeration problem,” J. Molec. Struct. 413-414(1997):227-239.

3220. D. Fuhrmann, Ch. Woll, “The microscopic origins of sliding friction: a spectroscopic approach,” New J. Phys. 1(17 December 1998):1.1-1.9; http://uclibs.org/PID/711.

3221. G. Witte, D. Fuhrmann, Ch. Woll, “Low-energy molecular vibrations investigated by inelastic scattering of He atoms,” Chem. Phys. Lett. 265(7 February 1997):347-352.

3222. G. Witte, Ch. Woll, “External vibrations of hydrocarbons on Cu(100),” J. Chem. Phys. 103(1 October 1995):5860-5863.

3223. J. Weckesser, D. Fuhrmann, K. Weiss, Ch. Woll, N.V. Richardson, “Photoemission from long chain alkanes adsorbed on a metal surface and the electronic structure of trans-polyethylene (-CH2-)n,” Surf. Rev. Lett. 4(1997):209-218.

3224. A.J. Groszek, “Selective adsorption at graphite/hydrocarbon interfaces,” Proc. R. Soc. London A 314(1969):473-498.

3225. Maria Grosse-Rhode, G.H. Findenegg, “Formation of ordered monolayers of n-alkanes at the cleavage face of nickel chloride,” J. Colloid. Interface Sci. 64(April 1978):374-376.

3226. H.K. Christenson, D.W.R. Gruen, R.G. Horn, J.N. Israelachvili, “Structuring in liquid alkanes between solid surfaces. Force measurements and mean-field theory,” J. Chem. Phys. 87(1 August 1987):1834-1841.

3227. R.G. Horn, J.N. Israelachvili, “Molecular organization and viscosity of a thin film of molten polymer between two surfaces as probed by force measurements,” Macromolecules 21(1988):2836-2841.

3228. R.G. Horn, S.J. Hirz, G.H. Hadziioannou, C.W. Frank, J.M. Catala, "A reevaluation of forces measured across thin polymer films: nonequilibrium and pinning effects," J. Chem. Phys. 90(1 June 1989):6767-6774.

3229. A. Yethiraj, C.K. Hall, "Monte Carlo simulation of hard chain-hard sphere mixtures in slitlike pores," J. Chem. Phys. 91(15 October 1989):4827-4837.

3230. W.G. Madden, "Monte Carlo studies of the melt-vacuum interface of a lattice polymer," J. Chem. Phys. 87(15 July 1987):1405-1422.

3231. Charles Tanford, "Micelle shape and size," J. Phys. Chem. 76(12 October 1972):3020-3024.

3232. P. Smith, R.M. Lynden-Bell, W. Smith, "The behavior of liquid alkanes near interfaces," Molecular Physics 98(2000):255-260.

3233. Kim Bolton, Sylvie B.M. Bosio, William L. Hase, William F. Schneider, Kenneth C. Hass, "Comparison of explicit and united atom models for alkane chains physisorbed on α-Al_2O_3 (0001)," J. Phys. Chem. 103(1999):3885-3895.

3234. P. de Sainte Claire, K.C. Hass, W.F. Schneider, W.L. Hase, "Simulations of hydrocarbon adsorption and subsequent water penetration on an aluminum oxide surface," J. Chem. Phys. 106(1 May 1997):7331-7342.

3235. D. Fuhrmann, Ch. Woll, "Damping of external molecular vibrations at surfaces: alkanes on Cu(111) and Pb(111)," Surf. Sci. 368(1996):20-26.

3236. K.W. Herwig, Z. Wu, P. Dai, H. Taub, F.Y. Hansen, "Quasielastic neutron scattering and molecular dynamics simulation studies of the melting transition in butane and hexane monolayers adsorbed on graphite," J. Chem. Phys. 107(1997):5186-5189.

3237. J.S. Raut, D.S. Sholl, K.A. Fichthorn, "Molecular-dynamics simulation of structures and dynamics of n-butane adlayers on Pt(111)," Surf. Sci. 389(1997):88-102.

3238. Reinhard Hentschke, Britta L. Schurmann, "A molecular dynamics simulation of liquid benzene adsorbed on graphite," Surf. Sci. 262(1992):180-188.

3239. Shuichi Nose, Michael L. Klein, "Molecular-dynamics calculations for ethylene adsorbed on graphite," Phys. Rev. Lett. 53(20 August 1984):818-821.

3240. Steve Granick, "Dynamics of adsorption and desorption at polymer/solid interfaces," in Isaac C. Sanchez, ed., Physics of Polymer Surfaces and Interfaces, Chapter 10, Butterworth-Heinemann, Boston, MA, 1992, pp. 227-244.

3241. A.V. Kiselev, D.P. Poshkus, "Molecular-statistical calculation of the thermodynamic characteristics of adsorption of saturated and unsaturated hydrocarbons on graphitized thermal carbon black," J. Chem. Soc. Faraday Trans. II 72(1976):950-966.

3242. Moti Lal, D. Spencer, "Interactions of alkanes with graphite," J. Chem. Soc. Faraday Trans. II 70(1974):910-919.

3243. A.G. Bezius, V.P. Dreving, A.V. Kiselev, Russ. J. Phys. Chem. 38(1964):511.

3244. T.L. Sordo, J.A. Sordo, R. Florez, "Theoretical study of adsorption of hydrocarbons on graphite," J. Comput. Chem. 11(1990):291-296.

3245. S. Leggetter, D.J. Tildesley, "The computer simulation of adsorbed hydrocarbons," Molec. Phys. 68(1989):519-546.

3246. M. Salmeron, G.A. Somorjai, "Adsorption and bonding of butane and pentane on the Pt(111) crystal surfaces. Effects of oxygen treatments and deuterium preadsorption," J. Phys. Chem. 85(10 December 1981):3835-3840.

3247. R.M. Slayton, C.M. Aubuchon, T.L. Camis, A.R. Noble, N.J. Tro, "Desorption kinetics and adlayer sticking model of n-butane, n-hexane, and n-octane on Al2O3(0001)," J. Phys. Chem. 99(1995):2151-2154.

3248. B.A. Sexton, A.E. Hughes, "A comparison of weak molecular adsorption of organic molecules on clean copper and platinum surfaces," Surf. Sci. 140(May 1984):227-248.

3249. Reinhard Hentschke, Roland G. Winkler, "Molecular dynamics simulation study of the adsorption of chain alkanes from solution onto graphite," J. Chem. Phys. 99(1 October 1993):5528-5534.

3250. Gerhard H. Findenegg, Maria Liphard, "Adsorption from solution of large alkane and related molecules onto graphitized carbon," Carbon 25(1987):119-128.

3251. A.J. Groszek, "Preferential adsorption of normal hydrocarbons on cast iron," Nature 196(10 November 1962):531-533.

3252. A.J. Groszek, "Preferential adsorption of long-chain normal paraffins on MoS_2, WS_2 and graphite from n-heptane," Nature 204(14 November 1964):680.

3253. Jean-Louis Barrat, Lyderic Bocquet, "Large slip effect at a nonwetting fluid solid interface," Phys. Rev. Lett. 82(7 June 1999):4671-4674.

3254. S. Pricl, I. Fermeglia, "Virtual rheological experiments on linear alkane chains confined between titanium walls," Rheologica Acta 40(March 2001):104-110.

3255. http://www.siad.it/GASTEC/tabellauk.html.

3256. "Acetylene"; http://www.concoa.com/frames/technical/gases/acetylen.htm.

3257. Shuxia Yin, Chen Wang, Xiaohui Qiu, Bo Xu, Chunli Bai, "Theoretical study of the effects of intermolecular interactions in self-assembled long-chain alkanes adsorbed on graphite surface," Surf. Interface Anal. 32(August 2001):248-252.

3258. W.N. McDicken, Diagnostic Ultrasonics: Principles and Use of Instruments, Third Edition, Churchill Livingstone, New York, 1991.

3259. M. Minnaert, "On musical air-bubbles and the sounds of running water," Phil. Mag. 16(1933):235-248.

3260. W. Schaaffs, "Molecular acoustics," in K. Hellwege, ed., Atomic and Molecular Physics, Volume 5, Landolt-Bornstein, NY, 1967.

3261. B. Hadimioglu, J.S. Foster, "Advances in superfluid helium acoustic microscopy," J. Appl. Phys. 56 (1 October 1984):1976-1980.

3262. Rudiger Haberland, Lehrstuhl fur Feinwerktechnik, Universitat Kaiserslautern, 2002; http://www.uni-kl.de/FWT.

3263. J. Brainard, "Ultrasound prevents blood loss in surgery," Science News 153(27 June 1998):407.

3264. Stewart C. Bushong, Benjamin R. Archer, Diagnostic Ultrasound: Physics, Biology, and Instrumentation, Mosby Year Book, St. Louis, MO, 1991.

3265. Stephen P. Timoshenko, Theory of Plates and Shells, McGraw-Hill/United Engineering Trustees, New York, 1940; Ansel C. Ugural, Stresses in Plates and Shells, Second Edition, McGraw-Hill Higher Education, New York, 1998.

3266. Samuel Levy, Samuel Greenman, "Bending with large deflection of a clamped rectangular plate with length-width ratio of 1.5 under normal pressure," National Advisory Committee for Aeronautics (NACA), Washington DC, Technical Note 853, 1942; http://naca.larc.nasa.gov/reports/1942/naca-tn-853/.

3267. Prof. Dr.-Ing. Kai-Uwe Bletzinger, "Theory of Plates, Part II: Plates in bending," Lehrstuhl fur Statik, Technische Universitat Munchen, Lecture Notes, Winter Semester 2000/2001; http://www.statik.bauwesen.tu-muenchen.de/vorlesungen/plates.dir/plates_part2.pdf.

3268. Darrel R. Wur, Jimmy L. Davidson, Weng Poo Kang, Donald L. Kinser, "Polycrystalline diamond pressure sensor," J. MEMS 4(March 1995):34-41.

3269. Cherie Congedo, "Honeycomb Plate Properties," NASA Goddard Space Flight Center, 2001; http://femci.gsfc.nasa.gov/hcplate/.

3270. C.L. Mantell, Carbon and Graphite Handbook, Interscience Publishers, NY, 1968; Tuncer M. Kuzay, Zhibi Wang, "Review of Window and Filter Requirements for Commissioning of the Advanced Photon Source Insertion Device Beamlines. Table 10. Vapor Pressure of Graphite," Advanced Photon Source, Argonne National Laboratory, LS Note 236, 2 June 1994; http://www.aps.anl.gov/techpub/lsnotes/ls236/ls236.html#table10.

3271. Linus Pauling, College Chemistry, Third Edition, W.H. Freeman and Company, San Francisco, 1964.

3272. V. Piacente, G. Gigli, P. Scardala, A. Giustini, G. Bardi, "Vapor pressure of C-70 fullerene," J. Phys. Chem. 100(6 June 1996):9815-9819.

3273. S.H. Schwartz, A. Fardi, K. Haghighat, A. Langereis, H.T. Schmidt, H. Cederquist, "The Absolute Vapor Pressure of C60 and Arq+C60 Collisions,"; http://www.vacuum.org/nccavs/hci_2000/187Cederquist2.pdf.

3274. "Research Areas. Directed Energy Interactions with Surface. Fullerenes As Precursors for Diamond Film Growth," Chemistry Division, Argonne National Laboratory; http://chemistry.anl.gov/surfaces/fullerenes.html.

3275. A.V. Hamza, G.D. Kubiak, R.H. Stulen, "The role of hydrogen on the diamond C(111)-(2x1) reconstruction," Surface Sci. 206(1988):L833-L844.

3276. B.D. Thoms, J.N. Russell Jr., P.E. Pehrsson, J.E. Butler, "Adsorption and abstraction of hydrogen on polycrystalline diamond," J. Chem. Phys. 100(1 June 1994):8425-8431.

3277. D.D. Koleske, S.M. Gates, B.D. Thoms, J.N. Russell Jr., J.E. Butler, "Hydrogen on polycrystalline diamond films: Studies of isothermal desorption and atomic deuterium abstraction," J. Chem. Phys. 102(8 January 1995):992-1002.

3278. Jesper Wengel, "Nucleic acid nanotechnology — towards Angstrom-scale engineering," Org. Biomol. Chem. 2(2004):277-280; http://www.rsc.org/CFmuscat/intermediate_abstract.cfm?FURL=/ej/OB/2004/b313986g.PDF.

INDEX

A

Abortive karyogamy, 172
Abuse, 169, 196, 205, 206
Accident, 196, 204-206
Acetobacter xylinum, 114
Acetylene, 66, 132, 133, 161, 215, 225-228, 230-233
Acetylene decomposition, 225, 227
Acoustic cavitation, 225, 232
Acoustic control pulse energy, 227
Acoustic frequency, 225, 226, 232
Acoustic heating, 232
Acoustic signals, 126, 132, 133, 225, 226
Acoustic torque and fluid streaming, 232
Acoustic transducer and pressure bands, 225-227
Acoustic transducer for power and control, 225-231
Active or passive, 146
Active subunit, 3, 153, 155, 160, 163, 166, 167, 172, 177, 196-198
Active subunits complexity, 163
Active subunits scale, 163
Active subunits type, 163
Adamatzky, Andrew, 29
Adami, Christof, 12, 14, 179
Adams, Bryant, xix, 4, 157, 159
Adams, Michael, 161, 177
Adams, Scott, xix
Additive mechanosynthesis, 168
Additive synthesis, 168
Addressable protein targeting, 111
Adenovirus, 102, 105
Advanced Automation for Space Missions, 43, 79, 189
Advanced Mechatronics Laboratory, 33
Advanced Microsystems Laboratory, 117
Advanced Technology Program, 139, 184
Aerobacter aerogenes, 221
AFM, 67, 117, 159, 182, 183, 208
African elephant, 219
African giant pouched rat, 220
African wild dog, 220
Age and gender distributions, 190
Age at first reproduction, 175
Age for maturity, 175
Agency of Industrial Science and Technology, 26, 117
Agent-based, 182
Age of menarche, 186
Agile assembly architecture, 116
Agile Assembly project, 116
Agoric algorithm, 182
Agoric system, 28
AGV, 56
AI, xvii, xviii, 28, 37, 85-87, 153, 195, 196
Aiken, Howard, 209
AIST, 33
Akin, David L., 193
Alaska pipeline, 37
Alberti, Patrizia, 111
Alexandrian water clock of Ctesibus, 1
Alexandridis, 67
Algae, 79, 101, 156, 166, 199
Algorithmic chemistry, 119
Algorithmic replication, 18
Alkadophilus™, 199, 203
Allan Hills meteorite, 177
Allison, Truett, 219
Allometric scaling laws, 175, 176
Allopoietic machine, 145
Alternative history, 209
ALU, 195
Amabilino, David, 94
American beech, 219
American Chemical Society, 108
American elm, 219
American holly, 219
American Model Builder, 35
American Plastic Bricks, 35
Ames Research Center, 81
Ami-Lac, 35
Amino acid, 91, 97-101, 109-111, 113, 114, 119, 161, 162, 176, 177, 207
Amoeba dubia, 156
Amoeba proteus, 108, 156
Amoeba Robot project, 34
Amorphous computing, 182
AMP, 97
Amplication, 170
Analog replication, 168
Analog specification, 163
Analytical Engine, 208, 209, 217
Anaphase, 106
Anderson, Poul, 19
AND gate, 9, 114, 125
Andrews McMeel Publishing, 2
Angelucci, Rocky, xix
Animal breeding, 172
Anker, 35
Antibiotics, 105, 109, 113, 172, 199
Antibody binding, 113
Anti-crossbreeding, 154
Antikythera computer, 1
Anti-mRNA, 153
Antisense RNAs, 105
Ant-size robot, 116
Apollo Moon Program, 201
Apoptosis, 105

Apple II, 195
Apple Worm, 12
Appropriate automation, 27
Arabidopsis thaliana, 156
ARAMIS, 36
Arbib, Michael, 11, 38
Arbib machines, 38
Archimedes, 1
Architecture for machine replication, 6
Arctic fox, 220
Arctic ground squirrel, 220
Arizona State University, xix
Arnold, Marc E., 125
Array, xvii, 4, 10, 11, 13, 29, 35, 41, 51, 53, 57-59, 64, 67, 79, 80, 87, 92-94, 110-113, 117, 118, 136, 142, 146, 151, 161, 182-184, 186, 193, 194, 225
Arrival date, 208
Artificial atoms, 159
Artificial automata, 2, 6
Artificial biological replicators, 108-110
Artificial biorobots, 108
Artificial cells, 13, 108, 109, 161, 225
Artificial cellular replicators, 101
Artificial chemistry, 119
Artificial chromosomes, 64, 108, 110
Artificial diatom patterns, 115
Artificial DNA structures, 112, 113
Artificial intelligence, xvii, 26, 34, 36, 38, 42, 43, 67, 68, 145, 162, 195, 196, 198, 205
Artificial Intelligence Laboratory, 34, 67, 68, 162
Artificial kinematic replicators, 107
Artificial life, xvii, xix, 1, 12, 14, 18, 54, 55, 60, 108, 146, 149, 150, 157, 180, 206
Artificial Life Journal, 108
Artificial life program, 1, 108
Artificial life simulation, 12
Artificial living plant, 19, 20, 25, 180
Artificial macromolecular machines, 118
Artificial mechanoenzymes, 112
Artificial microbes, 108, 110, 114
Artificial organism, 13, 17, 55
Artificial programmable self-replicating manufacturing systems, 201, 206
Artificial protocell, 110
Artificial replicator, 4, 119, 149, 153, 154, 162, 170, 173, 174, 195-197, 201, 207, 208
Artificial reproducer, 4
Artificial viroids, 102
Aryananda, Lijin, 69
Asexual reproduction, 149, 157, 172
Asian elephant, 219
Aspen Institute, 198
Assembler casings, 125
Assembler design notes, 223-234
Assembler scalability, 224
Assembler simulation, 135
Assembler wall dimensions, 224
Assemblers have not yet been demonstrated, 208
Assembly (cf. fabrication), 89
Assembly device, 55, 57, 136, 140, 141, 168
Assembly line, 3, 26-28, 66, 79, 122, 138, 182, 194, 195
Assembly mechanism style, 165
Assembly module, 190, 191, 192
Assembly of nanoparts without fabrication, 120
Assembly of nanoscale building blocks, 183
Assembly of parts, 26, 95
Assembly process style, 168
Assembly robot, 26, 40, 45, 136-138, 151
Assembly sector, 49, 51, 86
Assembly station, 55, 57, 75, 122, 138, 139
Assisted replication, 63, 103
Assisted-reproduction, 150
Associator, 147
Assumptions and design tradeoffs explicitly stated, 215
A Study On Safe Nanotechnology, 198
Asynchronous cellular automata, 12, 83
A Tale of Two Cities, 116
Atkinson, William, 119
Atom count, 134, 161, 224, 233
Atomic conveyor belt, 118
Atomic Energy Commission, 5
Atomic holography, 118
Atomic separator, 52
ATOMS project, 117
ATP, 97, 101, 102, 107, 111, 112, 144, 184
Attila, 68
Attractor, 148, 149, 154, 173, 180, 215
Attractor-based heredity, 148
Attractor-based systems, 149
Audit trails, 168, 197
Authorization codes, 169
Auto- (clarified), 90
Auto-assisted reproduction, 150
AutoCAD, 184
Autocatalysis, 4, 11, 21, 90, 91, 95, 96
Autocatalytic assembly, 166
Autocatalytic chemical networks, 181
Autocatalytic cycles, 96, 168
Autocatalytic networks, 91, 95, 96
Autocatalytic polynucleotide system, 96
Autocatalytic rate constant, 96
Autocatalytic reaction, 91, 95, 150
Autocatalytic reaction networks, 150
Autocatalytic replication, 154, 172
Autocatalytic replicators, 157
Autocatalytic sets of proteins, 148
AutoDesk, 184
Autofac, 19, 196
Autogeneric system, 55
Automata replication, 5, 179
Automata theory, 5, 11, 63
Automated assembly, 3, 27, 28, 49, 56-58, 144, 208
Automated fabrication, 64
Automated factory, 19, 25-28, 34
Automated Machine Shop, 28
Automated microassembly, 116, 117
Automated part assembly, 57
Automated planning, 28, 57
Automated robot-building factory, 208
Automated work cells, 28
Automatically guided vehicle, 56
Automatic factory, 20, 25
Automobile assembly lines, 195
Autonomous, xviii, 1, 16, 18, 19, 30, 33-36, 42, 44-46, 49, 51, 60, 63, 69, 73, 75-78, 81, 85-87, 90, 95, 101, 102, 104, 109, 112, 119, 133, 147, 148, 153, 154, 157, 162-165, 170, 175, 176, 178, 180-182, 184, 190, 195, 197, 204-208
Autonomous kinematic replicator, 77, 176
Autonomously powered, 164
Autonomous macroscale replicator, 1
Autonomous replicator, 76, 77, 208
Autonomous replicons, 102
Autonomous robotic factory, 78

Autonomous robotics, xviii, 81
Autonomous self-extending machine, 78
Autonomous self-replicating electromechanical intelligences, 76
Autonomous self-replicating robot, 75, 76
Autonomous system, 33, 34, 36, 42, 154
Autonomous Systems Engineering Laboratory, 33, 34
Autopoiesis, 145
Autopoietic machine, 12, 145
Autopoietic reproduction, 145
Autopoietic system, 89
Autoproductive, 170, 171
Autoproductive vs. auxilioproductive, 171
Auto-replicable RNA, 102
Auto-reproduction, 150
Auxesis, 167
Auxeticity, 167, 170, 195
Auxetic replication, 167, 170
Auxilioproductive, 171
Auxon, 53, 54, 175, 220
Avena sativum, 156
Axolotl, 174
Azobacter chroococcum, 221

B

Babbage, Charles, 85, 208-210, 217
Baboon, 220
Bachand, G.D., 113
Bacillus subtilis, 221
Backward chaining, 202, 215
BACs, 110
Bacteria as physical system components, 114
Bacterial artificial chromosomes, 110
Bacterial ribosome, 96-99, 219, 221
Bacteriophage, 94, 103, 108, 110, 115, 156, 199, 221, 228
Badertscher, A., 13
Bagley, Richard J., 96
Ball, Philip, 95
Baltimore, David, 174
Bankard, Jim, 71
Banks, Jessica, 11, 68
Banzhaf, Wolfgang, 96
Barricelli, Nils, 12, 150, 160
Barros, Emanuel F., xix
Bartel, David P., 96
Base excision repair, 110
Base-pair mismatch correction systems, 110
Basic component, 60, 61
Batch Trojan generator, 205
BattleBots, 154
Bayko, 35
B-DNA, 92
Beam-based machine replication, 117
Beam lithography, 116, 117
BEAM robot games, 2
Bedau, Mark A., xvii, xix, 108
Bedford College, 21
Beef, 203
Behavioral information, 155
Belcher, Angela M., 115
Bell Aircraft Corporation, 20
Bell Laboratories, 65, 94, 111
Bell Telephone Laboratories, 12
Belousov-Zhabotinsky reaction, 95
Benner, Steven A., 177
Benson, Eric, 3
Bererton, Curt, xix, 67, 68
Bererton self-repairing robots, 67, 68
Bergstrom, D.E., 110
Berkeley, Edmund C., 159
Bernal, J.D., 2, 35
Bernstein, Jeremy, 5
Berserker, 38
Berube, David M., xix, 204, 212
Best, Robert G., xix
Beuchat, J.-L., 14
Big brown bat, 220
Bigelow, 8
Bi-gender, 172
Billeter, Martin, xix, 101
BILOFIX, 35
Binary fission, 82, 104, 107
Binet, J.P.M., 186
Binet's formula, 186
Bing's Structator, 35
Binnig, Gerd Karl, 202
BioBricks, 114
BioCyc, 109
Bioengineered self-replicating viruses, 110
Bioethics Statement of Principles, 198
Bio-inspired systems, 149
Biological clock, 169
Biological Parts, Registry of Standard, 114
Biological replicator, 101, 108-110, 146, 157, 164, 170, 173-176, 193, 195, 198, 199
Biological virus, 12
Biologically-inspired microscale robots, 148
BioMEMS device, 114
Biomining, 199
Biomolecular-directed positional parts assembly, 110
Biomorphic machine, 29, 148
Biomorphic survival law, 147
Bioremediation, 198, 199
Biorobot, 108
Biorobotics, 55
Biotechnology, 58, 89, 104, 110, 112, 184, 196, 197, 205, 207
Biotechnology replicators, 196
Biovorous ecophagy, 170
BioWall, 13
Biphase assembler, 140, 141, 195
Birnavirus, 104
Birol, I., 173
Birth factory, 159
Birth-immature replicator, 170, 186-188
Birth-mature replicator, 170, 186-188
Bishop, Forrest, xix, 29-31, 135, 136
Bishop overtool universal assembler, 135
Bishop, Robert H., 46
Bishop rotary assembler, 136
Bishop's XY active cell and cell aggregate, 30
Black cherry, 219
Black hole, 178
Black walnut, 219
Black willow, 219
Blacksmith's tools, 171
Block assemblers, 122, 136
Blockmen, 35
Blueprint, 6, 10, 16, 78, 82, 153, 155, 162, 163, 169, 172, 197, 204
Blue whale, 219
Bock, Edward, 193
Boeing, 64, 184, 185, 208
Boerlijst, Maarten, 96

Bogdanov, A.A., 145
Bohringer, Karl F., xix, 146, 150, 183
Bohringer taxonomy of microassembly, 150, 151
Bojinov, Hristo, 32
Boland, Thomas, 67
Bonner, John Tyler, 175
Bootstrap, 26, 35-37, 44-46, 51, 55, 64, 67, 78, 116, 138, 139, 141, 181, 193, 214
Bootstrap-capable system, 214
Bootstrapping sequence, 138
Born pregnant, 187
Bose-Einstein condensates, 118
Boston University, 34, 114
Bostrom, Nick, xix
Boto river dolphin, 220
Bottom-up, 108, 144, 171, 177
Boundary, 82, 145, 147, 159, 160, 168, 171, 189
Boyce, Chris, 38
Bracewell, Ronald N., 38
Bradbury, Robert J., xix, 103, 112
Bradley, William E., 40, 152
Bradley self-replicating teleoperated machine shop, 40, 41
BRAL, 35
Brandeis University, xix, 64
Brandon, Robert N., 146
Braun, Erez, 111
Brazilian tapir, 219
Breivik, Jarle, 95
Brevundimonas diminuta, 162
Brik-O-Built, 35
Brill, David, 12
Brin, David, xix
Brio, 35
Bristle Blocks, 35
British Association for the Advancement of Science, 208
British Interplanetary Society, xix, 39
Brittleness, 172
Broadcast architecture, 17, 51, 107, 120, 125, 129, 132, 133, 138, 153, 170, 196, 199, 206, 215
Broadcast architecture for control, 132, 133, 196, 199, 215
Broadcast instructions, 125, 126, 133, 153, 216
Brody, James P., 228
Brooklyn College, 23
Brooks Living Machines Program, 68
Brooks, Rodney, 67-69, 162
Brownian motion, 14, 153
Brownian self-assembly, 90
Browning, Iben, 20
Browning unnatural living state, 20
Brown, James H., 170
Brown University, xix
Brunel University, xix
Brunner, John, 12
Buckley, William R., xix, 12
Buddhist text, 116
Buildability, 215, 216
Builderific, 35
Building block, 29, 56, 58, 64, 68, 78, 91-93, 110-114, 125, 127, 135, 163, 165-168, 183, 191, 192, 195, 206, 207
Buildo, 35, 175
Bulk fluid and laminar flows, 227
Burch, John, xix, 123
Burger, John, 12, 156
Burke, Jim, 42
Burks, Arthur W., xix, 5, 6, 8, 24, 157
Bushy stunt virus, 102
Butler, Samuel, 2, 3
Byl, J., 12
B-Z structural transition in DNA, 111

C

CA, 8, 11, 13, 28, 29
Cabanis, Pierre, 2
CAD, 28, 64, 135
CAE, 28
Caenorhabditis elegans, 167
Cairns-Smith, A.G., 7
Calcium, 48, 113, 167, 177
Calder, Nigel, 37, 38
California Institute of Technology, xix, 42, 135
California Polytechnic State University, xix
California State University at Chico, xix
Calutron, 37
Calvin, M., 95
CAM, 28, 135
Cambrian explosion, 69
Cambridge University, 65
Cam-driven manipulation, 124
Canadian lynx, 190, 191
Canalization, 172
Cann, Alan J., xix, 104
Cannon, Robert, 43
Canny, John, xix, 65, 66
Capek, Karel, 2, 20, 169
Capsid, 94, 101-103, 115, 211
Capsomeres, 102
Carbon nanotube, 111-114, 126, 133, 212, 225, 228
Carbothermic process, 53
Carlton, Celeste, xx
Carnegie Mellon University, xvii, xix, 28, 33, 37, 67, 116, 117
Case, John, 16
Cased hydrocarbon assembler, 125-127, 187
Caselli, Giovanni, 209
Casting, 17, 40, 46, 49, 76, 77, 116, 168, 189
Castro, Carlos A., xix
Cat, 115, 220
Catalytic molecules, 148
Catenane, 91, 93, 94, 113
Caviar, 203
Cavitation, 225-227, 232
cDNA, 174
CEBOT, 30
Cell cycle, 104, 105, 115, 170
Cell division, 103-105, 167, 177, 219
Cellicon Inc., 114
Cell Matrix™, 14
Cell metabolic engineering, 109
Cell-powered mechanical motors, 114
Cell surface engineering, 109
Cell theory, 167
Cellular automata, xvii, 2, 3, 6, 8-14, 17, 28, 29, 35, 63, 67, 68, 79, 82, 83, 95, 118, 119, 135, 146, 147, 150, 159, 164, 170, 172, 179, 182
Cellular automata model of machine replication, 8-11, 14, 147
Cellular model of machine replication, 8-10
Cellular repair nanorobots, 195
Cellular robotic system, 30
Cellular spaces, 8, 11, 12, 29
Cellulose, 114, 211
CELSS, 79
Center for Automation Technologies, 117, 140, 144

Center for Bits and Atoms, 67
Center for Responsible Nanotechnology, 144, 204
Center of High Technologies in Manufacturing Systems, 117
Centralized logic replication, 82
Centrally-planned machinery, 172
Centromere, 105, 106
Certify guidelines compliance, 197
Cesarano, Joseph, III, 66
Chakrabarty, Ananda, 199
Chalcid wasp (*Encarsia formosa*), 220
Chang, Kenneth, 162
Channel and Net, 147
Chaos chaos, 156
Checkpoint, 105
Checksum correction, 173
Checksum function, 172
Chemical finite state machine, 85
Chemical oscillating reaction, 95
Chemical processing sector, 49, 50, 86
Chemical reaction automata, 109
Chemical replicator, 17, 139, 221
Chemical self-replicating system, 4, 91, 95
Chemical spatial pattern formation, 95
Chemical vapor deposition, 117
Chemotactic factors, 114
Chen, I.-Ming, 30
Chess, 12, 189, 195
Chessboard, 188
Chess-move calculation hardware chips, 195
Chess-playing computer, 195
Chicken, 156, 196, 203, 213, 220
Childs, Gwen V., xix
Chilomonas paramecium (Mastigophora), 221
Chimeric fusion proteins, 58
Chimeric pRNA, 111
Chimeric virus, 110
Chimpanzee, 220
Chinchilla, 220
Chirality, 114, 135
Chirikjian, Gregory S., xix, 17, 29, 32, 69-79, 150, 151, 186
Chirikjian self-replicating lunar factories, 76-79
Chlorarachniophyte, 107
Chlorella, 101
Chloroplast, 102, 107
Chou, Hui-Hsien, 12
Chromatid, 105-107
Chromatin, 105
Chromosome, 56, 64, 103-108, 110, 146, 155, 172
Chromosome engineering, 110
Cicchetti, D., 219
Ciliates, 148
CIM, 28
CimStation Robotics, 184
Citric acid cycle, 148
Clarke, Arthur C., xxi, 38
Classical theory of self-replication, 5-18, 145
Clathrate, 93
CLBs, 80
Clean manufacturing and pollution-free operation, 215
Clemson University, xix
Cliff, Rodger A., 44, 45
Closed Environment Life Support Systems, 79
Clostridium botulinum, 221
Closure condition, 41
Closure engineering, 4, 6, 39, 145, 180-182
Closure index, 182
Closure theory, 145, 180-182
CMU, xvii, xix, 28, 34
CMV, 103
CNC, 27
CNTs, 113
Codd, E.F., 11, 13
CODES Lab, 34
Cog, 68
CoinStruction, 35
C. oligotrophus, 162
Collagen, 114, 211
Collins, Charles Michael, 54
Collins fabricator, 54
Collins, Mike, xix, 65
Collins patents on reproductive mechanics, 54, 55
Colombano, Silvano P., xix, 80, 81
Colorado State University, xix
Comb drive, 183
Command and control system, 48
Commercially nonviable, 175
Commodore PET/CBM, 12
Commonwealth Club, 44
Community diversity, 190
Community robodynamics, 20
Compartmentalization, 101, 104
Compartmentation, 160
Competitive exclusion, 190
Complementarity, 82, 90, 96, 148, 168
Complexification, 174
Component analysis, 16
Composable structures, 166
Compound interest, 188
Compustat selection experiments, 115
Computational astrophysics, 195
Computational modeling, 14, 91, 216
Computational modeling of self-assembly processes, 91
Computational Nanotechnology Project, 135
Computational simulations of artificial replicators, 119
Computer-aided assembly planning, 214
Computer-aided design, 135
Computer-aided manufacturing, 135
Computer-assisted, 153
Computer control, 20, 51, 56, 57, 136, 138, 139, 141
Computer-integrated manufacturing, 28
Computer Science and Artificial Intelligence Laboratory, 67, 68
Computer virus, 12, 157, 196, 205
Configurable logic blocks, 80
Confined-fluid density layering, 228
Confluent states, 8
Conformational switch, 91, 94, 95, 103
Connection Machine, 133
Connector subsystem, 80
CONRO, 33
Consensus-copy correction, 110
Constructible machine, 6
Construction (defined), 89
Construction C10, 35
Construction error, 172
Construction machine, 15, 60-63
Construction-style assembly, 168
Construction toys, 35
Constructional universality, 6, 10, 17
Construct-O-Craft, 35
Constux, 35
Contact guidance, 114
Continuous extrusion system, 127

Continuous model, 6, 14
Control autonomy, 46, 153, 170, 205
Controller subsystem, 75, 80
Convergent assembly, 93, 122, 123, 125, 141-143, 168, 178, 185, 190-194, 224
Convergent assembly factory length, volume, and replication time, 192
Convergent assembly manufacturing systems, 185
Convergent assembly nanofactory systems, 125, 141, 191, 193
Convergent assembly process, 122, 141, 195
Converter, 147
Conveyor, 26, 53, 79, 114, 118, 120-122, 138, 159, 179, 194, 211
Conway, 11
Cook, Matthew, 111
Cooperative reverse engineering, 16
Copik, Alicija J., 114
Coppinger, Robert J., 25
Copy error, 173
Copy number control, 105, 110, 168
Core Wars, 12
Cornell Nanofabrication Facility, 183
Cornell University, xix, 78
Corynebacterium diphtheriae, 221
Cotton, 20, 203
Cousins, 96
Cow, 101, 177, 219
Cowen, Richard, 177
CPU, 161, 209
Crane, H.R., 95, 191
Craver, Tom R., 112
Cresswell, H.A., 23
Creutzfeldt-Jakob disease, 101
Criminal prosecution, 197
Criswell, David, 36, 64, 193
CRN, 144, 204
Cross, 35
Crossing the Darwinian threshold, 101, 174
Crossley, Maxwell J., 91
Cryptography, 11
Cryptomonad, 107
Crystal Robot, 33
CSAIL, 68
Cuburo, 35
Cumings, John, 212
Cushing, Andrew, 75
Custom DNA, 108
Cuza University, 81
CVD, 67, 117, 129
Cyanobacteria, 101, 162
Cybernetic control, 154
CYC Project, 196
Cyclodextrin nanotube, 94
Cytokinesis, 106

D

Damage tolerant, 124
Damha, Masad J., 92
Danforth, Stephen C., 65
Dangerous kinds of nanomanufacturing systems, 206
Dangerous replicators, 204
Dangerous self-replicating nanomachine, 206
Dangerous version, 206
Danielli, J.F., 108
Darbro, Wesley A., 132, 187, 188, 189
Darling, R.B., 183
DARPA, 31, 33
Dartmouth Robotics Lab, 33
Darwin, 2, 12
Darwinian threshold, 101, 174
Dassault Systems, 184
Data cache, 39, 155
Data for replication time and replicator mass, 219-221
Data storage capacity of the human brain, 155, 195
Daughter device, 126, 129, 132-135, 153, 155, 167, 169, 170, 172, 186, 188, 223, 227
Davies, Paul, xix, 38
Da Vinci, Leonardo, 185
Dawkins, Richard, 4, 10, 146, 148, 150, 167
Dawkins classification of replicators, 146
Decentralized replication, 166
Decider, 146, 147
Decoder, 9, 75, 147
Deep Blue, 195
Defect mechanism, 195
Deflagration, 226, 232
De Forest, Lee, xxi
DeHon, Andre, 95
Deinococcus radiodurans, 110, 114, 155
Del Monaco, James, 73
De Moivre, A., 186
Demonstrate the design is safe, 215
Demonstration, xvii, 18, 19, 34, 42, 44-46, 76, 79, 91, 95, 116, 179, 186, 201, 202, 204, 205, 208, 213
Demonstration of feasibility, 202-204
Demultiplexor, 111, 126, 127, 131, 213
Dendrimer, 91-93, 111
Dendrimeric oligonucleotides, 92
Dendrimer self-assembly, 93
Deneb/IGRIP, 184
Dennis Kunkel Microscopy, Inc., 105
Density-independent population growth, 190
Density of the assembler, 223
Density oscillations, 228
Der Zauberlehrling, 155
Descartes, Rene, 1, 2
Description-based reproduction, 155
Descriptive process information, 155
Desert replicator, 25, 53
Designable self-assembling molecular machine structures, 91
Design errors make the analysis inherently worthless, 210, 211
Design for analysis and validation, 214
Design for assembly, 28, 184, 214
Design for manufacturability, 37
Design for manufacturing/assembly, 214
Design for nonevolvability, 10, 215
Design guidelines, 176, 197
Design is too obvious, 204, 212
Design notes, 223
Design precedes construction, 201, 202
Design space, 4, 54, 55, 61, 89, 90, 145-147, 149, 150, 152, 153, 167, 172, 173, 176, 185, 191, 195, 202, 209, 210, 215, 217
Design space of cellular automata, 147
Design space of mechanical kinematic replicators, 152-174, 191
Design tradeoffs in nanofactory assembly process specialization, 194, 195
Desktop, xix, 14, 33, 65, 67, 116, 117, 123, 140, 195, 220
Desktop assembler, 116, 140, 195
Desktop factories, 116, 220
Desktop manufacturing, 117, 122
Desktop mobile manipulators, 33
Desktop molecular manufacturing appliance, 123
Desktop Rapid Prototyping Millirobots project, 116

Desktop 3-D printer, 65
Desorption regime, 229
Deterministic parallel microassembly, 151
Deutsch, D., 179
Developmental information, 155
Development principles, 197
Devore, J., 11, 13
DFA, 28
DFM/A, 214
D'Herelle, F., 102
D'Holbach, Baron, 2
Diamond, xvii, 89, 93, 110, 113, 116, 119, 127, 129, 132-135, 158, 166, 194, 202, 203, 207, 208, 213, 214, 224, 226, 229-234
Diamond mechanosynthesis, 110, 158, 166, 207
Diamondoid, 93, 119, 125-127, 129, 135, 137, 144, 165, 207, 211, 215, 225
Diamondoid networks, 93
Diatom nanotechnology, 115
Dick, Philip K., 19, 196
Dickens, Charles, 116
Didinium nasutum (Ciliata), 221
Difference Engine, 209
Differential analyzer, 5
Digital life, 14
Digitally signed, 169
Digital organism, 12
Digital replication, 168
Digital rights management, 169
Digital specification, 162, 163
Digital worm, 12
Dilbert, 2
Dilts, D.M., 28
Diplococcus pneumoniae I, 221
Diplococcus pneumoniae II, 221
Dip-pen nanolithography, 67, 183
Directed evolution in bacteria, 113
Directed nanoassembly of nanoparticle, 115
Directed self-assembly, 95, 110, 137, 166
Directly replicating, 151
Direct self-replication, 166
Discard rate, 191
Discounted present value, 175
Discover magazine, 53
Discrete replicator, 14, 148, 160, 167, 168
Disney, 154
Disruptive technology, 201
Distributed logic replication, 82
Distributed robotic system, 34
Distributor, 147
DLR, xix
DMD, 64
DNA, 2, 4, 6, 7, 15, 17, 57, 58, 82, 90-97, 101-114, 119, 133, 136, 139, 146, 148-150, 153, 155-157, 162, 168, 171-174, 177, 179, 182, 183, 195, 197, 198, 212, 228
DNA arrays, 111
DNA assisted-reproduction, 150
DNA-based actuator, 110-113
DNA-based chemical replicators, 17
DNA-based dendrimers, 92, 93
DNA-based ink, 112, 183
DNA-based molecular construction, 112
DNA-based nanomechanical devices, 111
DNA based nanoscale devices, 111
DNA-based sliding strut actuator, 112
DNA-based structures, 57, 58, 182
DNA-based strut, 112
DNA complementarity, 168
DNA device, 112
DNA-directed 2-D array, 111
DNA double crossover, 92
DNA-guided assembly of proteins, 111
DNA hand, 111
DNA lattice, 111
DNA ligase, 92, 112
DNA-molecule inchworm motor, 111
DNA nanoconstruction, 92
DNA nanomotor, 112
DNA nanoscaffolds, 112
DNA nanotechnology, 92, 111
DNA octahedron, 93
DNA packaging motor, 102, 111
DNA piston, 111
DNA polymerase, 6, 104, 107
DNA replication, 15, 105, 113
DNA replication complex, 113
DNA reproduction, 150
DNA scaffolds, 58, 94, 111, 113
DNA self-assembly, 111
DNA structure, 92, 112, 113
DNA tiles, 111, 112
Docoslis, Aristides, 67
Dogaru, Radu, xix
Domino, 3, 4, 80, 148
Dongles, 169
Donkey, 219
Dorf, Richard C., 46
Dorset Press, 1
Double-band operation, 227-229, 231
Double crossover, 58, 92
Double-tripod, 130
Dow Chemical, 65
Draper Fisher Jurvetson, xvii
Drexler, K. Eric, xix, 7, 11, 96, 110, 118-130, 132, 136, 140-142, 159, 168, 170, 171, 178, 182, 194, 195, 197, 201-207, 210, 211, 214, 220, 221, 224, 234
Drexler extruding tube assembler, 120, 121
Drexler generic assembler, 120
Drexler manipulator arm, 182, 221
Drexler minimal assembler, 127-129
Drexler molecular assemblers, 119-125, 127-129
Drexler nanofactory, 121-125
Drill press, 40
DRM, 169
Drosophila melanogaster, 156
Drugs, 11, 169, 199, 206, 225
Drum, Ryan W., 115
Dry/artificial, 171
Dublin City University, xix
Duke University, 112
Dynamic tests, 135
Dyson, Freeman J., xix, 20, 24, 25, 35, 44, 53, 101, 196-198
Dyson, George, 4
Dyson terraforming replicators, 24, 25

E

Early design will not speed development, 204, 208-210
Ease of reprogramming, 214
Eastern American mole, 220
Eastern hemlock, 219
Eastern red cedar, 219
Eastern white pine, 219

Easy Fit, 35
E-beam lithographic resolution, 117
E-beam lithography, 116
Ebefors, T., 116
EBID, 117, 168
Ebolavirus, 156
Echidna, 220
Ecole Polytechnique, xix, 13
Ecophagy, 170, 204, 205
Ecopoiesis, 79
Ecopoiesis Test Bed, 79
Edison, Thomas Alva, 29
Edmonds, Bruce, 168
EFAB™, 52, 66
Effector automata, 29
Efficient replicator scaling conjecture, 145, 178
Efstathiou, J., 157
Egea Biosciences, 108, 198
Egg, 25, 107, 170, 174, 196, 203, 213, 216
Egg machine, 25, 196
Eggs, 79, 203
Eigen, Manfred, 12, 96, 172, 173
Einstein diffusion velocity, 233
Einstein-Smoluchowski diffusion equation, 229
Einstein-Stokes equation, 231
Eitech, 35
Electrodeposition microfabrication, 52, 66, 118
Electromagnetic enrichment, 37
Electromechanical relay, 79, 209, 217
Electromechanical replicator, 24, 58, 59, 60
Electromechanical self-replication, 67
Electron beam induced deposition, 117
Electron beam stereolithography, 117
Electrophoresis, 17, 49, 66, 67, 92, 139
Electrostatic motors, 116, 135
Electrostatic self-assembly, 95
Elektromehaniskais konstructors, 35
Elementary building blocks, 64
Elephant mitochondria, 107
Elephants lacking tusks, 172
Elevator, 131, 132, 134, 223, 226, 227
Elevator drive screws, 223
Elevator plate, 132, 134, 223, 226, 227
Eli Lilly, 199
Ellenbogen, James, 116
Ellington, Andrew D., 148
Ellis, Matthew, xix
Elowitz, Michael B., 114
Embedded replication veto, 154
Embedded switches, 95
Embodied evolution, 18
Embryogeny, 157, 174
Embryonics, 13, 14, 195
Emission of waste products, 171
Enceladus replicator, 24, 25
Encoder, 147
Encrypted instruction sets, 169
Endosymbiont, 107, 172
Endosymbiosis, 107
Endy, D., 110
Energy closure, 64, 65, 170, 180
Energy consumption, 170
Energy cost of molecular manufacturing, 233, 225
Energy Department, 108
Energy efficiency, 164, 165, 225, 233
Energy system, 48
EngeneOS, 108, 109
Engineered genetic blinkers, 114
Engineered self-replicating bacteria, 109
Engines of Creation, 119, 120, 197, 204
ENIAC, 5, 208
Ensemble replication, 148, 163
Entropy of substrate, 158, 159
Enveloped virus, 102
Envelope expansion velocity, 189
Environmental fixture requirement, 158, 159
Environmental partitioning, 158, 173
Environmental Protection Agency, 199
Enzymatic allostery, 94
Enzyme-free self-replication, 95, 96
EPA, 199
EPFL, 13
Epicurus, 3
Epigenesis, 63, 149
Epilogue, 19
EPO, 199
Erber, T., 29
Erector®, 35
Erewhon, 2
Erkman, Suren, xix
Error-correcting code, 110
Error-correcting polymerases, 110
Error correction, 54, 109, 110, 169
Error correction mechanisms, 169
Error detection and correction, 110, 224
Error free, 197
Error-free self-replication, 89
Error, manufacturing, 169
Error-prone self-replication, 89
Error rate, 65, 99, 110, 119, 122, 127, 149, 172, 195, 224
Errors in fabricated parts, 169
Error tolerance, 60, 109, 154, 169
Erwinia carotovora, 221
Erythromycin, 199
Erythropoietin, 199
Escherichia coli, 103-105, 109, 114, 156, 162, 164, 165, 221
E-Spaces, 136
ESPREAD, 92
Ethical impact of machine replicators, 199
Euclid, 185
Euglena gracilis (Mastigophora), 221
Eukaryote, 96, 97, 99, 101, 104-107, 109, 133, 157, 166, 170, 172, 197
Eukaryotic cell cycle, 105, 170
Europa, 177
European Center for Living Technology, 108
European Community, 198
European hedgehog, 220
European IST Program, 117
European Union, 108
Evans, Glen, 108, 109
Evodevo, 115
Evolution, xvii, xviii, 2, 4, 6, 10-12, 14, 15, 17, 18, 25, 63, 64, 69, 78, 89, 93, 95, 102, 107-109, 113, 115, 146, 148, 149, 150, 155, 163, 172-174, 176, 177, 179, 181, 182, 190, 196, 197, 199, 208, 213, 215, 216
Evolutionary algorithms, 18, 149, 173
Evolutionary computation, 149
Evolutionary robotics, 18, 64
Evolution of diversity, 172
Evolution of life, 196
Evolvability, 10, 15, 16, 111, 153, 154, 172-174, 176, 179

Evolvability scales inversely with size, 176
Ewaschuk, Robert, 14
Exacto, 35
Excitation-threshold-fatigue model, 6
Exemplify backward chaining in design, 215
Exemplify programmable molecular positional assembly, 212, 213
Exemplify self-replication in a molecular manufacturing system, 213
Existence proof, 161, 180, 208
Expandagon, 35
Experimental evolution, 190
Expert system, 25, 181, 184
Explicit-implicit coding, 150
Explicit process information, 155
Exponential assembly, 4, 17, 55, 136, 138-141, 184
Exponential growth, 17, 19, 36, 78, 79, 115, 138, 139, 148, 187-190
Exponential kinematic self-replication, 186, 188
Exponentiating, 42, 43, 46, 120, 189
Extended-maturation replicator, 170, 186-188
External veto authority, 154
Extracellular matrix, 114
Extraction ratio, 158
Extruder, 147
Extruding brick, 126, 127, 129, 130, 132
Extruding daughter device, 223
Extruding tube, 120
Extrusion spring, 134, 223
Ezy-Bilt, 35

F

F1-ATPase protein, 113
Fabricating machine, 54, 55
Fabrication (cf. assembly), 89
Fabrication device, 140, 141, 168
Fabrication sector, 49, 50, 86
Fabricator, 39, 40, 54, 67, 136-139, 141, 142, 166, 204
Fabricator robot, 39
FAC, 35
Facton, 41
Factor VIII, 199
Factory, 2, 3, 11, 17, 19, 20, 25-28, 34, 36, 37, 40, 42-51, 53, 64, 67, 75-79, 81, 85-87, 97, 101, 104, 106, 115, 116, 120-122, 125, 132, 136-140, 142, 151-153, 156, 159, 161, 166-169, 175, 180, 181, 183-186, 188, 189, 191-197, 199, 204, 206, 208, 214, 215, 219, 220
Factory field, 47, 48
Factory model, 46, 121, 186
Factory production line, 195
Factory replication, 47, 49, 51, 85, 120, 121, 136-140, 152, 167, 195, 196, 215
Factory-mode molecular manufacturing, 191
Fail-safe, 154
Fallacy of the substrate, 145, 157, 178-180
Falling-domino automaton, 3
Fanuc factory group, 27
Farmer, J. Doyne, 96
Fat fingers, 207
Fatty acid synthase, 177
Fault-tolerant, 11, 13, 29, 57, 58, 109, 141, 142, 149, 182, 195
FDA, 196
FDM, 52, 64
Fear of self-replicating systems, 204
Fearing, Ronald S., xix, 116, 150, 178
Feasibility, xvii, 5, 42, 44-46, 76, 78, 79, 89, 119, 148, 198, 201-204, 206-208, 210-215, 217
Feasibility demonstration, 44-46, 76, 201, 202
Feasibility of molecular assembler or nanofactory, 201, 212, 213
Fecundity, 41, 146, 170, 172, 175, 186, 190
Feedstock, 25, 36, 41, 46, 47, 52, 64, 65, 80, 98, 115, 122, 125-129, 132, 133, 136, 140-142, 153, 159, 162, 165, 166, 176, 183, 204, 224-227, 231, 232
Feedstock bottleneck, 224
Feedstock import through boundary, 159
Feldmann, Richard J., 108
Fenniri, Hicham, xix, 91-93
Ferris, James P., 177
Fertility test, 45, 76, 172
Fertility vs. energy consumption, 170
Feynman, Richard P., 114-117, 201, 205, 211
Feynman Grand Prize, 125
Feynman hierarchical machine shop, 115, 116
Feynman machines, 38
FIB, 117
Fibonacci, Leonardo, 185
Fibonacci number, 185, 186
Fibonacci's rabbits, 185-187
Fibrillogenesis, 114
Fibroblast, 114
Fibroplasia, 114
Fiddlestix, 35
Fidelity, 4, 109, 110, 146, 155, 156, 169, 172, 173
Field-programmable gate array, 13, 195
Financial world, 188
Fine motion controller, 120, 125
Finite state automaton, 8, 118
Finite state machines, 85
Fire, 4, 148, 154, 206
Firewood, 203
First replicators, 120, 196
Fischer Technik, 35, 68
Fission, 82, 101, 104, 107, 167, 178, 204
Fixed location, 159, 162, 164
Fixed-size genomes, 174
Fixture, 40, 69, 71, 72, 100, 151, 158, 159
Fixture Acquisition, 159
Fixture-based replication, 100, 151
Fixtures, 26, 41, 69-71, 77, 151, 152, 158, 159
Flexible assembly station, 57
Flexible assembly system, 28
Flexible manufacturing system, 19, 25-28, 56, 195
Flexible nanomanufacturing, 195
Flexonics, 65, 66
Flexsim, 184
Flibs, 12
Flores, Ricardo, xix, 102
Flowering dogwood, 219
Fluidic agitation, 151
Fluidic self-assembly, 90, 94
FMS, 27, 56
Focused ion beam assisted deposition, 117
Focused-ion-beam CVD, 67
Fontana, Walter, 119
Force closure, 182
Ford's River Rouge complex, 180
Foresight Guidelines on Molecular Nanotechnology, 14, 15, 179, 197, 198, 204, 205
Foresight Institute, xix, 120, 125, 197
Form closure, 182
Formose reaction, 148
Formose system, 172
Forrest, David, 197

Forrest, Stephanie, xix
Forrester, A.T., 37
Forward chaining, 202
FPGA, 13, 14, 80, 195
Fractal robot, 29, 31, 33, 57
Fractiles, 35
Fractional-gender, 172
Fractum self-repairing machine, 29
Frameshift, 109, 157
Frankenstein, 2
Fraser, C.M., 93, 94, 108
Fredkin cell space, 11
Fredkin parity rule, 11
Freeform fabrication, 37, 38, 52, 64, 66
Free-range self-replicators, 205
Freitas, Robert A., Jr., xx, 4, 5, 12, 25, 30, 32, 35, 38, 39, 43, 44, 49, 51, 52, 77, 81, 82, 112, 113, 117, 127, 130, 132, 138, 141, 158, 159, 167, 170, 175, 178, 180, 186, 188, 189, 191, 195, 197, 198, 201, 205-207, 213, 223, 224
Freitas atomic separator replicator, 52
Freitas biphase assembler, 140, 141
Freitas factory replication system, 49-51, 136
Freitas interstellar probe replicator, 38-40
Freitas-Merkle map of the kinematic replicator design space, 145, 152-174
Friedman, George, xviii, xix, 17, 37, 42, 161, 170, 180, 181
Friedrich-Schiller University, 108
Frontier Log Building, 35
Frosch, Robert A., xix, 42-45, 51
Fruit fly, 156, 220
Fruit fly (*Drosophila*), 220
Fujita, H., 183
Fujitsu Fanuc, xix, 26, 27, 184, 208
Fukuda, Toshio, 30
Fullerene, 92, 94, 111, 114, 234
Functionality matrix, 61, 62, 181
Function-replicators, 157
Fungus, 79, 101, 166, 199
Furley, David J., 3
Fused deposition modeling, 52, 64

G

G0 phase, 105
G1 phase, 105
G2 phase, 105
Galago, 220
Galaxy-sized replicator, 178
Gallus domesticus, 156
Game of Life, 11
Ganesan, Oprema, 71
Ganti, Tibor, 96
Garbage, 128, 130, 171
Gardner, Timothy S., xix, 114
Gas phase solid freeform fabrication, 52
Gas phase vs. solvent phase manufacturing, 225
Gastrointestinal microflora, 203
GBPs, 113
Gecko, 220
Gendered replicators, 172
Gendericity, 172
Gene-like replicators, 149, 154
General Dynamics, 29, 79
General Electric Company, 199
General-purpose assembler, 121, 126, 195
General-purpose factory, 49, 97, 194
General-purpose replicating system, 194
Generational and gestational fecundity, 170
Generational longevity, 170
Generation-limited replication, 188, 189
Generation time, 169, 170, 175
Generation time vs. gestation time, 170
Generic molecular assembler, 120, 125, 126
Genetic algorithm, 6, 12, 28, 56, 64, 146, 147, 196
Genetically engineered bacteria, 161, 198
Genetic engineering, 108, 199, 207
Genetic information, 18, 105, 109, 155, 177
Genetic therapies, 110, 170
GeneWriter™, 108
Genghis, 68
Genome, 4, 7, 13, 55, 63, 69, 90, 101, 103-105, 107-110, 114, 148, 149, 154-157, 162, 163, 173, 174, 177, 179
Genomic redundancy, 165, 173
Genotype, 10, 13, 15, 148, 170, 173, 174
Genotypic replicators, 148
GEOMAG, 35
Geometric accessibility to products during manufacture, 214
Geometrical derivation of assembler dimensions, 223
George Mason University, xix
Georgia Institute of Technology, xix, xx, 66
German National Research Centre for Information Technology, xix
Germ-line or dead-end, 146
Gerovichev, Oleg, 71
Gerrold, David, 12
Gershenfeld, Neil, 67
Gestation time, 170, 186, 219
Ghadiri, M.R., 91, 96
Giant sequoia, 219
Gibbs free energy, 227
Gibson, William, 209
Gilbreath, William P., 5, 51, 132, 158, 170, 175, 186, 190, 191, 201
Gillett, Stephen L., 25
Gimzewski, James K., xix, 212
Giraffe, 219
Global ecophagy, 204, 205
Globus, Al, 30, 31
Glucose engines, 164
Goat, 220
Goddard, Robert, 208, 209
Goddard, William A., 135
Goddard proposed assembler simulation study, 135
Goel, Narendra S., 29
Golay, Marcel, 155
Gold, 38, 66, 91, 111, 113-117, 203, 230
Goldberg, Ken, 150
Goldberg, Robert B., 162
Gold-binding protein, 113
Golden hamster, 220
Golden mean, 185
Golden number, 185
Golden ratio, 185
Golden section, 185
Goldstine, Herman H., 5, 8
Golem, 2
GOLEM Project, 64, 65
Goncz, Doug, 40
Gordon, Richard, 115
Gorilla, 170, 219
Goulian, M., 108

GPS, 49
Gracias, David H., 95
Graded induction, 163
Granularity, 158, 159, 171
GRAPE, 195
Graph automata, 29
Graphene, 126
Gray goo, 170, 204, 205
Gray-Scott model, 95
Gray seal, 220
Gray wolf, 220
Griffith, Saul, xix, 23, 65, 67, 82-85, 94, 95
Griffith mechanical self-replicating strings, 82-85
Griffith self-replicating wire, 84, 85
Gross Domestic Product (GDP), 201
Ground squirrel, 220
Growth, 11, 17, 19, 25, 36, 46, 48-51, 53, 54, 58, 63, 78, 79, 90, 93, 101, 103-105, 109, 110, 113, 115, 117, 121, 138, 139, 147-149, 154, 159, 160, 167, 170, 174-176, 185-190, 194, 196, 199, 226
Guanosine triphosphate, 97
Gubrud, Mark, 118
Guided self-assembly, 95
Guidice, Rick, 43
Guinea pig, 220
Guo, Peixuan, 111
Gupta, S., 229
G-wires, 92

H

Haas Automation, Inc., 27
Hadamard matrix transforms, 111
Haenni, J.-O., 14
Hagen-Poiseuille law, 227
Haldane, J.B.S., 179
Hall, J. Storrs, xix, 29, 125, 136-138, 140, 192-195
Hall factory replication system, 136-138
Hammerhead ribozymes, 102, 103
Hamster, 220
Hard-coded assembly, 165
Hardin, Garrett, 207
Harmful biological replicator, 199
Hart, Edwin J., 226
Harvard University, 34, 114
Harvey, I., 18
Hashimoto, Takashi, 119
Hasslacher, Brosl, xix, 29, 35, 146-148
Hasslacher-Tilden MAP survival space, 146, 147
Hatakeyama, Toyomasa, 119
Hauser, 12
Hawk, 3, 220
Heat shock protein, 113
Hecht, Michael H., 109
Heer, Ewald, 42
Heifer Project, 196
Heifers, 203
Helicase, 104
Helium, 128-130, 158, 232
Hemmerling, Armin, 29
Hemophilus influenzae, 156
Henderson, Eric R., 92
Henry, Joseph, 209
Hepadnavirus, 104
Hereditary potential, 149, 150
Hereditary process, 148
Hereditary variants, 172
Heredity, 148-150, 172
Heritable mutation, 4
Herman, Gabor T., 4
Hero of Alexandria, 1
Herpes simplex, 102
Herpesvirus, 105
Heterochrony, 159, 174
Hewitt, Judson T., 36, 193
Hewlett-Packard, 65, 66
Hexlo, 35
HGH, 199
Hierarchical assembly, 95, 191
Hierarchical convergent assembly, 122
Hierarchical machine shop, 115
Hierarchical self-assembly, 92, 95
Higher School of Economics, Moscow, xix
Ho, Wilson, 207
Hoenigsberg, H., 174
Hofbauer, J., 96
Hofstadter, Douglas, 3, 119, 180
Hogan, James P., 44
Hogeweg, Pauline, 96
Hogg, Tad, xix, 32, 95, 191
Hoggatt, V.E., Jr., 188
Hokkaido University, 34
Holistic, 148, 149, 168
Holland, John, 17
Holland, Owen, 29
Holliday junctions, 92
Honeybee (*Apoidea apis*), 220
Horizontal gene transfer, 156, 174
Horn, T., 92
Horse, 199, 219
Hosokawa, K., 34
H.R. 766, 198
HSV, 103
Hu, Evelyn L., 115
Hughes, James, 205
Hui, E.E., 58
Hull, D.L., 146
Human birth rate, 170
Human-equivalent computing, 195
Human growth hormone, 199
Human hepatitis delta virus, 102
Hummingbird, 220
Humpback whale, 219
Hungarian Academy of Sciences, xix
Hupp, Jon A., 12
Husbands, P., 18
Hutton, Tim J., xix, 11, 119
Hybrid cellular-kinematic model, 15
Hybrid systems, 153
Hybrid wet-dry, 158, 159, 171
HYDRA Project, 34
Hydrocarbon, 94, 113, 117, 125-127, 129-133, 135, 161, 162, 187, 211, 213-215, 224, 225-227, 229-231
Hydrocarbon assembler, 125-127, 130-135, 187, 214
Hydropathic index, 110
Hypercycle, 96
Hyperredundant manipulators, 165
Hysteresis, 190

I

IBEA, 108
IBM, xix, 12, 27, 93, 117, 182, 183, 195, 202, 209
IBM 7090, 12
ICES Cubes, 34
I-Cubes, 34
IEEE Nanotechnology Council, xix
Ignatiev, Alex, 64
Ikegami, Takashi, xx, 119
Illegal drugs, 169
ImagiBRICKS™, 35
Imai, Katsunobu, 12
IMM, 120, 197
Immature replicator, 170, 186-188
Immortal cell lines, 170
Impossibility, 2, 3, 28, 90, 116, 149, 173, 180, 185, 201, 204, 206-209, 214, 217, 223
Inchworm, 111, 116
Indefinite hereditary, 150
Indirectly replicating, 75, 151, 152
Indirect self-replication, 166
Industrial development kit, 25
Industrial ecology, 28
Industrial park, 175
Industrial revolution, 67
Inferential reverse engineering, 3, 16
Infinite regress, 3, 16
Influenza, 102, 156, 221
Information closure, 65, 90, 180, 181
Information relativity, 180
Ingestor, 147, 158, 168
Ingestor modality, 168
Inherently safe, 4, 10, 11, 17, 107, 133, 138, 153, 164, 170, 199, 205, 206, 215
Inherent safety, 15, 153, 199
Innovation On Demand, Inc., 117
Input transducer, 147
Inspection of parts, 26
Institute for Biological Energy Alternatives, 108
Institute for Machine Tools and Industrial Management, 117
Institute for Molecular Manufacturing, xx, 120, 197
Instructed mixture paradigm, 91
Insulin, 199
Insurance, xxi, 197
Integrated Genomics Inc., 108
Intelligent Autonomous Systems Engineering Laboratory, 33
Intelligent manufacturing systems, 28
Intelligent Systems Institute, 33
Interactor, 146
Interest rate, 188
Interferons, 203
Intermediate robot replication, 152
Internal transducer, 147
International Space Station, 79
Internet worm, 156
Interphase, 105
Interreplicator information transfer, 174
Interstellar, 37-39, 189, 191, 219
Interstellar probe populations, 191
Interworld Productions, 136
Iowa State University, xix
IRobot, 68
Irresponsible hobbyists, 204
Irreversible mutations, 173
ISI, 33
Isotope separation, 52
ISS, 79
Iterated design bootstrapping, 138
Iterative arrays, 11, 117
Iterons, 105
Itoh, Toshihiro, 182

J

Jacobson, Homer, 23, 24, 220
Jacobson, Joseph, 65, 67, 109, 110, 114, 155, 184
Jacobson locomotive toy train replicator, 23, 24
Jacobstein, Neil, xx, 197, 198, 201
JACS, 96
Jaeger, L., 96, 112
Jaguar, 220
Janusonis, Stepas, 168
(Japan) National Institute of Advanced Science and Technology (AIST), 33
Japanese Space Agency, 44
Jastrow, Robert, 2
Jeon, K.W., 108, 208
Jet aircraft, 161
Jet Propulsion Laboratory, 42
Jig, 26, 40, 56, 57, 111, 129, 134, 137, 140, 159, 166, 167, 168, 180
Jig borer, 40
JohnnyVon program, 14
Johns Hopkins University, 32, 46, 69, 70, 71, 72, 73, 74, 76, 77, 78, 151
Johnson, Robert R., 159
Johnstone, Bob, 44
JOVO, 35
Joy, Bill, 205
Joyce, Gerald F., 4, 89, 91-93, 96, 155
JPL, 42
Jumbleness, 158
Junior, 35
Jurvetson, Steve, xvii

K

Kaku, Michio, 38
Kangaroo, 220
Kant, 3
KAPLA, 35
Kasparov, Gary, 195
Katawa, Satoshi, 66
Kauffman, Stuart A., 96, 150
KCA, 29-31, 35, 58, 79-82, 135, 157
KCA-based replicator, 157
KCA cell, 29-31, 35, 80, 81, 135
Kemeny, John, 2, 7, 19
Kenyon, Ralph E., 3
Kessler, N., 113
Khoshnevis, Behrokh, 65
Khushf, George, xx
Kiln, 53
Kime, Charles R., 182
Kinematic-cell product, 171
Kinematic cellular automaton, 28-35, 58, 68, 79-82, 135, 157, 182
Kinematic machine, 4, 6-8, 10, 17, 19, 24, 29, 45, 118, 119, 145, 179, 199
Kinematic machine replication, 4, 7, 10, 17, 19, 24, 45, 118, 145, 179, 199
Kinematic manipulator, 159
Kinematic model, 7, 8, 10, 15, 16, 63

Kinematic model of machine replication, 7, 8
Kinematic replicator, 7, 8, 19, 25, 28, 55, 65, 70-74, 77, 89, 107, 145, 146, 152, 153, 155, 157-159, 166, 176, 178, 191, 199, 201
Kinematic replicator design space, 55, 145, 146, 152-174
Kinematic self-replication, xviii, 10, 107, 186, 188, 199
Kinetids, 148
Kinetochore, 106
Kinsey report, 5
Kismet, 68
Kitagawa, Masaya, 71
Kleene, Stephen C., 2
Klein, Jacob, 229
Knapp, Loren W., xx
Knex, 35
Knight, Tom, 109
Knott, Ron D., xx, 185, 186
Knowledge units, 196
Knutson, Roger M., 166
Koch's Postulates, 12
Kokaji, S., 29
Komerath, Narayanan M., xx
Kondo, T., 114
Koopman, D.C., 229
Koops, Hans, xx, 117
Kovacs, G.T.A., 183
Koza, John R., xx, 13, 146
Krummenacker, Markus, xx, 111, 162
Krylov, S.M., 127
K-selection, 190
Kubrick, Stanley, 38
Kumacheva, Eugenia, 229
Kunkel, Dennis, xx, 104
Kurzweil, Raymond, xx, 198
Kvasnicka, Vladimir, 119

L

Laboratory for Molecular Robotics, 89, 162
Lackner, Klaus S., xx, 53, 193
Lackner-Wendt auxon replicators, 53, 54, 175, 220
Lactobacillus acidophilus, 221
Ladybug, 220
Laing, Richard A., xvii, xx, 5, 6, 15-17, 29, 44, 118, 119, 148
Laing kinematic automaton system, 118
Laing molecular tapeworms, 118, 119
Laing's self-reproduction by self-inspection, 17
Lamarckian, 174
Lamarckian evolution, 174
Laminated object modeling, 64
Landers, Richard R., 29
Landman, Uzi, 231
Langmuir-Blodgett films, 90
Langton, Chris G., xx, 11-13, 17, 157
Langton's SR loop, 12
Laptop computer, 155, 203
Laser, 48, 49, 52, 64, 66, 67, 77, 83, 115, 226
Laser-based stereolithography, 67
Laser direct metal deposition, 64
LASY, 35
Lathe, 27, 40, 41, 45, 67, 115, 186
Lathrop, George Parsons, 25
Lawrence, Jeffrey, 117, 177
Lawrence Livermore National Laboratory, 117
Laws of thermodynamics, 182
Leahy, William D., 206
Leaning Tower, 185
Learning, xvii, 42, 63, 68, 69, 147, 148, 149, 174, 212
Lee, C.Y., 16
Lee, Hyojune, 207
Legal impact of machine replicators, 199
Legal liability, 197
LEGO®, 1, 17, 33-35, 46, 65, 68-74, 76, 77, 79, 83, 94, 158, 162, 176, 208, 220
LEGO® animals, 34
LEGO®-based replicator, 34, 69-76
LEGO® car factory, 34
LEGO® factory, 34
Lego Lab, 34
Lehn, Jean-Marie, 91
Leibler, S., 114
Lenat, Douglas, 196
LEO, 78
Leonardo of Pisa, 185
Lesser short-tailed shrew, 220
Levy, Marrhew, 148
Lewin, Benjamin, 97, 100, 105, 106
Lewis, James B., xx
Lewis, Jennifer A., 66
Li, Jianwei J., 111
Liberty Logs, 35
Lichen, 101, 166
Life history strategies, 190
Lifespan, 53, 82, 170, 188
Life-synthesis, 108
Lifetime reproductive ratio, 170
Ligase, 92, 96, 112, 177, 221
Light-driven molecular assembly, 118
Lights out, 27
Lim, Jonathan, 74
Limited assemblers, 198
Limited heredity, 148, 149
Limited-indefinite hereditary, 150
Limited-purpose replicators, 170
Limits to assembler scalability, 224
Limits to convergent assembly processes, 195
Limits to exponential kinematic self-replication, 188-191
Linares, Diego, xx
Lincoln Logs, 35
Lind, D.A., 188
Linear templating replication, 82
Linkoping University, 34
Liong, Tak, 74
Lipson, Hod, 4, 14, 64-67, 69, 78, 157, 159
Lipson self-extending machines, 78
LISP, 13
Literature and culture informing ethical analysis of nanotechnology, 199
Little brown bat, 220
Liverpool University, xix
Living machines, 68
Lizard Fire Studios, 123
Logical core architecture, 37
Logical universality, 6, 10, 17
Logic bomb, 12
Lohn, Jason, xx
Lohn, 29, 58, 59, 60, 146, 147, 169, 170
Lohn electromechanical replicators, 58-60
Lokon, 35
LOM, 64
Longevity, 146, 169, 170
Los Alamos National Laboratory, 147, 206
Lotka-Volterra model, 190

Loughborough University, xix
Low cost manufacturing, xvii, 196
Low Earth orbit, 36, 78, 181
Lowe, T.C., 35
Lozneanu, Erzilia, 81, 82
Lozneanu-Sanduloviciu plasma cell replicators, 81, 82
Lucas, Edouard, 185
Lucent, 65
Lucian of Samosata, 155
Ludwig Maximilians University, 111
Lugowski, Marek W., 29
Luisi, Pier Luigi, xx, 90, 108
Luksha, Pavel O., xix, xx, 3, 157, 173, 180
Lunar and Planetary Institute, 36, 64
Lunar ecopoiesis, 79
Lunar factory, 25, 36, 43-46, 48, 51, 63, 67, 76-79, 85, 87, 132, 140, 156, 175, 180, 184, 189, 219
Lunar power system, 63, 64
Lunar self-replicating factory, 17, 46-51, 76, 77, 85-87
Lunar station, 44
Lund, H., 18
Luxury automobile, 116, 203
Lymphocyte engineering, 109
Lynch, Ken C., 119
Lynx, 190, 191
Lyons, 35
Lyshevski, S.E., xix
Lysogenic cycle, 103
Lytic cycle, 103

M

M13 bacteriophage, 115
MAb, 113
MacDonald, Noel C., 183
Machi, Filip, 12
Machine Intelligence Corporation, 45
Machine life, 197
Machine-phase chemical synthesis, 119
Machine-phase nanotechnology, 182
Machine shop, 27, 28, 40, 41, 115, 175
MacLulich, D.A., 190
MacNicol, D.D., 93
Macroevolution, 190
Macroscale-inspired machinery, 204, 211, 212
MACs, 110
Mad cow disease, 101
Make Your Own Toys, 35
Malone, Evan, xx, 64, 153
Malthus, Thomas Robert, 189
Malthusian parameter, 190
Malware, 205
Mammalian artificial chromosome, 110
Manetico, 35
Mange, Daniel, xx, 12, 13
Manhattan Project, 5, 8, 201, 207, 216
Manipulator positional accuracy, 166
Manipulator-style assembly, 165, 166
Manipulator-type mechanism, 122, 165, 194, 195
Mano, 53
Manual operation, 28, 153
Manufacturability, 37, 57
Manufactured from scratch, 110
Manufacturing error, 169
Manufacturing-style assembly, 168
Manufacturing system, 2, 6, 15, 19, 25-28, 35, 37, 38, 43, 55, 56, 89, 117, 122, 124, 126-128, 131-133, 136, 139, 141, 152, 153, 157, 170, 172, 173, 175, 178-182, 185, 191-193, 195, 197, 201-203, 205-208, 212-216
Manufacturing system parameters, 124
MAP survival space, 146, 147
Marchal, Pierre, xx
Marder, Seth R., 66
Margolus, Norman, 29
Mark I, 209
Marklin Mehanotehnika, 35
MARS, 30
Mars, 24, 25, 35, 37, 78, 79, 177
Marshall Space Flight Center, 44, 189
Martel, S., 183
Martian meteorite ALH84001, 176
Martin, Martin C., xx, 69
Massachusetts Institute of Technology, xix, 67, 162
Mass-driver, 36
Massively parallel assembly, 141, 178, 182, 184, 216
Massively parallel manipulator arrays, 182-184
Massively parallel molecular manufacturing, 182-184
Massively parallel processing, 144, 168, 182
Materials depot, 46, 47
Materials flowthrough path length, 192
Materials handling, 26
Materials processing, 37, 46, 53
Materials Research Society, 183
Materials throughput speed, 192
Materials transport wall, 223, 224
Mathematical primer on self-replicating systems, 185
Matter closure, 180
Matter-energy storage, 147
Maturana, Humberto R., 145
Maurer, Brian A., 176
Mavroidis, Constantinos, xx, 112, 113
Maximum number of generations, 170
Maximum reliability during operation, 214, 215
MaxScript, 81
Maxwell, J., 66
McCarthy, Wil, xx, 159
McCaskill, John, 108
McCord, Richard L., 188
McCulloch-Pitts, 6
McIlroy, Doug, 12
McKendree, Thomas, 37, 193
McLellan, William, 116
McMullin, Barry, xx, 6, 146
Meccano®, 35
Mechalyst, 112
Mechanical allosteric enzyme, 94
Mechanical depassivation contamination, 234
Mechanical DNA-based actuator, 110, 111
Mechanical enzyme, 94, 119
Mechanical kinematic replicators, 191
Mechanically assembled monolayers, 100
Mechanically-threaded molecules, 93
Mechanical parts, 23, 91, 94, 95
Mechanochemistry, 125, 135
Mechanoenzyme, 112, 113, 141
Mechanosynthesis, xvii, 110, 119, 125, 127, 129, 132-134, 137, 138, 140-142, 158, 161, 166, 168, 178, 194, 207, 208, 214, 224, 233, 234
Mechanosynthetic tool tips, 133, 224
Mechatronical Secondary Vocational School, xix

Mechatronic, xix, 29, 32-34, 65, 69, 75, 76, 117
Medical nanorobotics, 33
MegaBloks, 35
Meiosis, 107
Mekanik, 35
Mek-Struct, 35
MEMbler™, 139
Membrane synthase ribozymes, 177
Meme, 13, 107, 148, 157
Memory, 7-14, 16, 20, 25, 32, 33, 41, 42, 45, 54, 55, 57, 66, 82, 83, 85, 105, 111, 114, 121, 126, 132, 135, 147, 155, 158, 161, 174, 195-197, 202, 209, 210
Memory tape, 7, 8, 10, 11
MEMS, xix, 58, 65, 114-116, 138-140, 144, 158, 159, 171, 183, 184, 204, 211, 225
Menarche, 186
Menopause, 170
Menstruation, 186
Merchant, M.E., 25
Mergny, Jean-Louis, 111
Merkle, Ralph C., xx, 4, 12, 38, 46, 112, 113, 122, 123, 125-127, 129, 130, 140, 141, 145, 152, 155, 162, 172, 178, 192, 193, 197, 198, 201, 202, 207, 210, 211, 213, 215, 216, 223
Merkle cased hydrocarbon assembler, 126, 127, 187
Merkle-Freitas assembler, 119, 125, 127, 130-135, 140, 156, 161, 164, 165, 171, 176, 223-234
Merkle-Freitas hydrocarbon molecular assembler, 130-135, 215, 221, 223-234
Merkle generic assembler, 125, 126
Merkle molecular assemblers, 125-127, 129-135
Merkle replicating brick assembler, 127-129
Merkur, 35
Mesoplasma florum, 109
Mesoscopic nucleic acid analogs, 95
Meszena, G., 170
Metall, 35
Metallus, 35
Metamorphic, 29, 32, 127
Metamorphosing robots, 58
Metaphase, 106
Metazoan, 107, 174
Methodology for unmanned manufacturing, 26
Mettrie, Julien Offroy de La, 2
M. genitalium, 108, 155
Michael, Joseph, xx, 29-30, 33, 57
Michael's fractal robot, 29, 30
Michelin, 27
Michener, James, 42
Michigan State University, xix, 33
Microactuators, 66, 116, 183
Microarrays, 116
Microassembly, 115-117, 144, 146, 150, 151
Micro Assembly Automation Laboratory, 117
Microbe-directed parts fabrication, 114
Microbial engineering, 109
Microbiomedical devices, 66
Microbivore, 195
Microcantilever, 111, 113, 182, 183
Microcar, 116
Micro Coliseum, 117
Microdynamic Systems Laboratory, 117
Microelectronics, 51, 56, 66, 95, 117, 144, 181
Microelectromechanical, xix, 67, 114, 116, 138, 139, 144, 184
Micro-electrophoretics, 66
Microfabrication, 52, 56, 66, 67, 118
Microfabricated probe array, 67
Microfactory, 117, 183
Microfluidics, 66, 132, 140, 141, 225, 228
Microfossils, 176
Microgear train, 116
Microgripper array, 151
Microgrippers, 116, 151
Microgyroscopes, 116
Microlithography, 183
Micro Machine Project, 116
Micromanufacturing, xix, 117
Micromechanical engineering, 116
Micromechatronics, xix
Micromirror, 67, 116
Micromotor, 116
MiCRoN Project, 117
Microoptics, 66
Micro-origami, 58, 95
Micropistons, 116
Micropolymerization, 66
Microprocessor active surface, 203
Micropumps, 66, 116
Microrobot, 36, 66, 33, 116, 183
Microrobot Project, 33
Micro rocket project, 116
Microscale manufacturing system, 170, 175
Microscale parts, 90, 183
Microscale replicator, 89, 160, 176, 181, 199, 208
Microscale robots, 148
Microscopic prayer books, 116
Microsensors, 116, 225
Microsoft Window, 196, 212
Microstereolithography, 66
Micro-STM, 183
Microtransducers, 116
Microvalves, 116
Middlesex University, xix
Milky Way galaxy, 178
Mill assembly mechanism, 194
Miller, James Grier, 146, 163
Miller critical subsystems of living systems, 146, 147
Miller, Rene H., 193
Millibot, 116
Millimeter-size robot, 116
Milling machine, 40, 41, 137
Millipede project, 57, 182, 183
Millirobot, 116
Millirobot desktop factories, 116
Mills, 1, 37, 67, 115, 122, 124, 125, 164-166, 180, 194, 195
Mill-style assembly, 165, 166
Mill-type mechanisms, 122, 124, 165, 194, 195
Mimetic replicators, 13
MinDART, 33
Mindstorm, 69
Miniature mobile robots, 116
Miniaturized factory, 116
Minifactories, 116
Minimal artificial microbe, 108, 109
Minimal assembler, 120, 127, 129, 130, 132
Minimal gene set, 108
Minimalist organism, 108
Mini Meta-Build, 35
Minimum and maximum size of kinematic replicators, 145, 176-178
Mining robots, 39, 49
Mini-plants, 25, 28

Ministry of International Trade and Industry, 26
Minnaert, M., 232
Minsky, Marvin, xx, 193, 195-197
Mirkin, Chad A., 67, 112, 183
Mironov, Vladimir, 67
Misuse, 197, 205
MIT, xx, 35, 65, 67, 68, 109, 110, 114, 116, 155, 184
MIT Media Lab, xx, 65, 155, 184
MITI, 26
Mitochondrion, 101, 106, 107, 156, 221
Mitosis, 105-107, 146
MITRE Corp., 116
MNT, xvii, 17, 197, 206
Mobile automata, 14, 29
Mobile robotics simulator, 184
Mobile robots, 18, 35, 53, 68, 87, 116
Mobility, 29, 147, 162, 188, 189, 204, 205
Models of self-replication and self-regulation, 198
Mode of dimensional specification, 162, 163
Mode of genomic heritability, 174
Modern Morecraft, 35
Modular arrays, 11
Modular assembly, 58, 93
Modular manufacturing, 25, 58, 163
Modular reconfigurable robot, 30, 33
Modular replicators, 148
Modular TRANSformer, 33
Module assembly time, 192
Moiety abstraction, 168
Moiety deposition, 168
Molecubotics, Inc., 111
Molecular assembler, xvii, xviii, 2, 4, 89, 90, 93, 100, 119, 120, 122, 125-127, 130-135, 140, 144, 151, 161, 164, 165, 170, 178, 201, 202, 204, 206-210, 212-217, 221, 223-227, 232, 233
Molecular assemblers are impossible, 206-208
Molecular assemblers are too dangerous, 204-205
Molecular assembly, 89, 111, 118, 121, 122, 124
Molecular automata, 89
Molecular building blocks, 91, 113, 127, 135, 163
Molecular camshaft, 112, 113
Molecular chaperones, 113
Molecular constructor, 126
Molecular ecosystem, 96
Molecular fabrication, 89, 136
Molecular feedstock, 115, 124, 125, 140, 142, 166, 183
Molecularly Precise Tool Project, 144
Molecular machine, 2, 15, 29, 91, 93, 94, 96, 97, 104, 111, 114, 118, 119, 140, 206, 207, 211, 212
Molecular manipulator arm, 119-121, 126
Molecular manufacturing, xx, xvii, 120, 122, 124, 126, 127, 131-133, 136, 141, 160, 161, 163, 164, 172, 178, 181, 182, 184, 191, 193, 197-199, 201-205, 207, 208, 210, 212-216, 225, 233
Molecular mechanical computer, 126
Molecular mills, 166, 194
Molecular motors, 103, 113
Molecular nanotechnology, xvii, 17, 37, 63, 92, 136, 196, 197, 199, 201-206, 210
Molecular necklace, 93
Molecular parts, 93, 96-100, 113, 119, 212, 213
Molecular positional assembly, 96, 117, 212
Molecular robotics, xix, 89, 162
Molecular scaffolding, 111
Molecular-scale self-replicating systems, 197
Molecular self-assembly, 90, 198
Molecular shuttle, 93
Molecular sorting rotor, 124, 125
Molecular tapeworms, 118, 119
Molecular tools, 119-122, 129, 130, 133, 134, 201, 207, 214
Molecule Robot, 33
Mole rat, 220
Monoclonal antibodies, 113
Mono-gender, 172
Monomer synthase, 177
Monotype electromechanical replicator, 59
Montemagno, Carlo, 113, 114
Moon, 17, 36-38, 42, 44, 48, 49, 51, 63, 79, 85, 201, 209
Moon, Daniel, 74
Moore artificial living plants, 19, 20, 25
Moore, Edward F., 11, 19, 20, 23, 25, 170, 180
Moore, Peter, 177
Moore's law, 35
Moratorium, 206, 207
Moravec, Hans P., xx, 28, 37
Morgan, Charles R., 25
Morgenstern, Oskar, 8
Morita, Kenichi, 12
Morowitz, Harold J., 24, 58, 59, 108, 208
Morowitz floating electromechanical replicator, 24
Morphable structures, 58
Morphogenesis, 34, 157
Morris, Harold C., 119
Morse, Samuel, 209
Mortality, 188, 189, 190
Moser, David, 13
Moses, J., 35
Moses, Matt, xx, 35, 60-63, 81
Moses, Melanie E., 170
Moses self-replicating construction machine, 60-63
Motile parts-assembly robot, 137
Motion planning, 32, 184
MotoSim, 184
Mountain beaver, 220
Mouse, 101, 114, 156, 220
Movable automata, 29
Movable cellular automata, 29
Movable finite automata, 29, 119
M phase, 105
mRNA, 97, 98, 100, 101, 104, 105, 113, 119, 120, 133, 153, 157, 179, 182
MRSI assembly robots, 151
mtDNA, 107
M-TRAN, 33
Mulberries, 203
Mule, 172
Mulligan, 67
Multicellular, 13, 69, 107, 148, 149, 163, 167, 169
Multicellular automata, 148, 149
Multigendered systems, 172
Multilevel genomic heritability, 174
Multiple utility of active subunits, 163
Multiple utility of passive parts, 162
Multiplication, 48, 149, 172, 189, 209
Multi-robot planning, 67
Multirobot systems, 33, 34
Multi-robot-without-fixture replication, 151
MUM, 26
Munich Microassembly Research, 117
Murata, S., 32
Mushegian, xx
Mushegian, Arcady R., 108, 109
Mushegian's minimal genome, 156
Musk shrew, 220
Mus musculus, 156

Mustafa, Tabish, 72
Mutually obligate virion-eukaryote symbiotes, 101
Mycobacterium tuberculosis, 221
Mycobiont, 101
Mycoplasma genitalium, 109, 155, 156, 177, 212
Mycoplasma mycoides, 179
Myhill, J., 11
Myxococcus xanthus, 160

N

NAC, 42
Nagoya University, xix, 117
Nagpal, Radhika, 95
Naked RNA virus, 110
Naked virus, 102
NAND gate, 80, 81, 114
Nannobacteria, 177
Nanoarchaeum equitans, 156
Nanobacteria, 160, 177
Nanobiology, 109
Nanoblocks, 141, 142
Nano cellular automata, 119
Nanocircles, 114
Nanocoils, 114
Nanocomputer, 121, 122, 141
Nanoconstructions, 58, 92, 93
Nanocrystals, 113-115
Nanoelectromechanical system, xix, 89, 140, 144, 184
Nanofactory, xvii, 4, 121-125, 141-144, 161, 163-165, 170, 181, 183, 185, 191-195, 204, 205, 208, 212, 215, 216
Nanofactory assembly process specialization, 194
Nanofactory-based molecular manufacturing systems, 181
Nanofactory workstation grid, 142
Nanofossils, 177
Nanofountainpen, 67
Nanohedra, 96
Nanohype, 204
Nanolithography, 67, 118, 144, 183
Nanomachine, 11, 89, 93, 110, 115, 119-121, 135, 169, 178, 182, 199, 205, 206, 211, 216
Nanomanipulator, 125, 135, 136, 166, 175
Nanomanufacturing, xix, 152, 183, 194, 205, 206
Nanomass, 204
Nanomechatronics, xix
Nanomedicine, 32, 35, 102, 114, 127, 155, 164, 167, 176, 195, 196, 210
Nanoparticle assemblies, 111
Nanoparts assembly, 112
Nanopart synthetases, 113
Nanoporous molecular crystals, 93
Nanoprocessor, 58
Nanorobotics, xix, 33, 37, 111, 211, 185, 195
Nanorobots, 19, 35, 38, 81, 89, 140, 195, 204
Nanorod, 117
Nanoscale array, 113
Nanoscale assembler, 97, 140, 144, 184
Nanoscale assembly, 58, 110, 115
Nanoscale devices, 58, 111, 201
Nanoscale machinery, 211
Nanoscale parts, 90, 112, 113
Nanostencil, 117
Nanosystems, 118, 120, 124, 126, 127, 129, 133, 164, 165, 178, 193, 194, 195, 202, 211, 217
Nanotechnology, xvii, xix, xxi, 17, 30, 37, 38, 44, 51, 60, 63, 89, 92, 110, 114, 115, 119, 125, 135, 136, 144, 146, 147, 158, 159, 171, 175, 176, 178, 180-182, 196-199, 201-206, 208, 210, 216
Nanotechnology replicators, 44, 175, 176, 196, 198
Nanotube, 91-94, 103, 111-114, 126, 133, 198, 203, 212, 225, 228
Nanotube self-assembly, 113
Nanotweezer, 112
Nanovesicle, 91
NanoWalker, 111, 183
Nanowire, 93, 111, 113-115
Napier University, xix
NASA, xvii, xviii, 3, 25, 28, 36, 40, 42-46, 51, 59, 60, 63, 76-79, 81, 85, 120, 132, 156, 170, 175-177, 179-181, 184, 188, 189, 201, 211, 219
NASA Advisory Council, 42
NASA Institute for Advanced Concepts, 78
NASA robot replication feasibility demonstration, 45
NASA self-replicating lunar factory, 156, 219
NASA Study Group on Machine Intelligence and Robotics, 42
NASA Summer Study on self-replicating systems (1980), 36, 42-51, 79, 184, 189
NAS Workshop, 177
National Academy of Sciences, 78, 176, 198
National Bureau of Standards, 202
National Institute of Advanced Science and Technology, xx
National Institute of Standards and Technology, 139, 184
National Nanotechnology Research and Development Act of 2003, 198
National Research Council (Italy), xix
National Science Foundation, 45, 198
Natural biological replicators, 101, 173
Natural self-replicating systems, 198
Nature, xx, 110
Navier-Stokes equations, 227
Near-field optical lithography, 66
Near replication of an ancestor, 173
Near replication of a parent, 173
Near-wall solvation forces, 228
Necessary degeneracy, 3
Necobo, 35
Nehaniv, Chrystopher L., xx
Nelson, B.J., 117
Nemes, Tihamer, 40
NEMS, xix, 89, 140, 144, 184
Neon, 125, 126, 129, 130
Neon pump, 125
Network connectivity, 168
Network model of self-replication, 119
Networks/clusters of workstation, 182
Neural network, 6, 64, 69, 148, 149
Neuronal system, 6
Neutral molecular beam deposition, 117
New Directions Workshop, 42, 63
New England Complex Systems Institute, xix
Newman, Tom, 116, 117
Newman, W., 38
New, Michael, 157
New Scientist, 66, 81
New York University, xix, 92, 111
NeXT, 27
NIAC, 78, 79
Nice-Dice, 35
Niche construction, 158
Nicotiana tabacum, 156
Niemeyer, Christof M., 92, 110
Nierenberg, William, 42
NIH, 108, 197, 206
NIH Guidelines on Recombinant DNA technology, 197
Nine-banded armadillo, 220
Nippondenso Co. Ltd., 116
Nissan, 26

NIST, 139, 144, 184
Niven, Larry, 43
Nobili, Renato, 11
Nomoto, Tsuyoshi, 119
Nonautonomous, 17, 51, 132
Non-auxetic replication, 167
Non-auxetic replicators, 170
Nonevolutionary algorithm, 173
Nonevolvability, 10, 172, 215
Nonevolvable design, 169
Non-gendered, 172
Non-Mendelian replicating oil droplets, 101
Nonparasitic, 166
Nonproductive replicators, 152
Nonreplicator product types, 170
Nonribosomal peptide synthetases, 101
Non-self, 6, 46, 132, 140, 152, 160, 161, 170, 171, 194
Non-trivial self-replication, 173
NOR gate, 114
North American opossum, 220
North Carolina State University, xix
Northern catalpa, 219
Northern white cedar, 219
Northwestern University, xix
Norton AntiVirus, 12
NOT gate, 125
Noyes, Richard Macy, 95
NSF, xviii, 34, 45, 63, 116, 198
Nuclear power plant, 48
Nuclear replicator, 178
Nucleic acids, 58, 91, 92, 94-96, 101, 102, 112, 113, 148, 155
Nucleobase amino acids, 91
Nucleoprotein-based nanoscale assembly, 110
Nucleotide, 55, 57, 58, 91, 92, 96-99, 101-104, 108-111, 148, 157, 161, 177, 179, 219
Nucleotide analogs, 96
Number of distinct onboard transformative processes, 168
Number of fertile mutant configurations, 172, 173
Number of manipulator types, 165
Number of onboard process energy types, 164
Number of vitamin parts, 161, 162
Nussinov, M.D., 25
Nutritional complexity, 162

O

Obsolescence, 175
Octane, 132, 133, 223-233
Offloading complexity, 213
Offspring fertility, 172
Offspring separability, 169
Oil-eating microbe, 199
Okapi, 219
Oko, 53
Okuma, Michio, 29
Oligonucleotide-directed self-assembly of proteins, 110
Oligotrophic, 177
Oliver, Barney, 42
Olympiadane, 94
Omni Magazine, 44
O'Neill, Gerard K., 35-37, 197
Ontogeny, 148, 149, 174
Oocyte, 107
Op-amp, 80, 81
Open-ended evolution, 10, 150, 155, 182
OpenMind Commonsense Project, 196
Operating-subsystem-in-process replication, 151, 186
Ophioglossum petiolatum, 156
Optimal foraging and environmental stress, 190
Orangutan, 220
Orbital tower, 37
Ordinary transmission cell states, 8
Organic templating, 93
Organismic model, 46, 120
OR gate, 125
Orgel, Leslie, 95
Origin of life, 11, 101, 160, 174
Orthomyxovirus, 104
Osaka University, 66, 67
Oscillating chemical systems, 95
Oscillating populations of microbes, 190
Ostrand, Thomas J., 11
Output port, 191-193
Output port areas, 192
Output transducer, 147
Ovaries, 107, 167
Override, 154
Overtool, 31, 135
Overtool universal assembler, 135
Owens, R.A., xx, 102
Owl monkey, 220
Oxford University Press, xx, 97, 100, 106

P

Packard, Norman, 108
Padilla, J.E., 96
Pajaro Dunes, 43
Paleolithic, 1
Paley, William, 2
Palikit, 35
Pangram, 180
Pantelegraph, 209
Pantograph, 115
Parabolic growth, 148, 190
Paradox, 5-7, 148, 205
Parallel assembly, xvii, 141, 144, 178, 182, 184, 216
Parallel manufacturing, xvii, 4, 145, 182, 184
Parallel micromanufacturing, 117
Parallel molecular Manufacturing, 182
Parallel operation, 55, 67, 117, 213
Parallel pick-and-place, 151
Parallel processing, 144, 168, 182
Paramecium aurelia (Ciliata), 221
Paramecium bursaria, 101
Parasite, 102, 155, 156, 161, 166, 190
Parasite-host interaction, 190
Parasitic reproduction, 101, 105, 152, 157, 166, 177
Parent-progeny relationship, 173
Pargellis, 12
Parham, Steven, 167
Partial closure, 170, 181
Partial information closure, 181
Particle device, 159
Parts assembler, 136, 137
Parts assembly, 41, 49, 80, 110, 112-114, 136-138, 180, 194
Parts bin, 94, 95, 162, 164
Parts count, 161, 176
Parts depot, 45, 47
Parts design, 125, 166
Parts fabrication, 28, 49, 50, 77, 114, 168, 180
Parts fabricator, 136-139
Parts forming, 25
Parts insertion, 113

Parts precision, 162
Parts presentation, 158, 162, 183
Parts production plant, 47
Parts-assembly robot, 136, 137
Parvovirus, 105
Pascal, Blaise, 187
Pascal's triangle, 186, 187
Passive constituent parts count, 161
Passive constituent parts types, 161
Passive constituents parts scale, 161
Passive parts, 153, 161, 162, 163
Passive parts complexity, 162
Patas monkey, 220
Pattee, H.H., 148, 182
Patterned Atomic Layer Epitaxy Project, 144
Paul, Natasha, 4, 91, 96, 155
Paving robots, 49, 51
Pearls, 203
Pecan, 219
PEMS, 67
Penicillin, 199
Pennsylvania State University, xix
Penrose block replicator, 21-23, 95, 208, 220
Penrose, Lionel S., 19, 21, 22, 59
Penrose, Roger, 21, 23, 58, 82
Pentium IV, 80
Peptide, 91, 96, 99-101, 108, 112, 113, 119, 148, 219
Peptide-based self-replicating systems, 91
Peptide nucleic acids, 91, 112
Performance of convergent assembly nanofactory systems, 185, 191-193
Periodic pulsers, 9
Perry, Joseph W., 66
Personal desktop 3-D printer, 65
Personal fabricators, 67
Personal factories, 64
Pesavento, Umberto, 11
Peterson, Christine, 198
Petunia parodii, 156
Pfeifer, Rolf, xx
Phanlanger, 220
Phares, Alain J., 186
Phenome, 17
Phenotype, 10, 11, 13, 15, 17, 146, 148, 172, 174, 176, 195
Phenotypic replicator, 148
Philopseudes, 155
PhiX174, 108
Phi X bacteriophage virus, 108
Phoenix, Christopher J., xx, 65, 126, 141-144, 149, 164, 172, 187, 193, 206, 207
Phoenix primitive nanofactory, 141-144
Photoautotrophic, 162
Photobiont, 101
Photocopier, 4
Photovoltaic, 48, 49, 63, 64, 77, 79
Phylogeny, 4, 10, 148, 149
Physarum polycephalum, 107
Physical mutation, 172
Physical product, 171
Physisorbed monolayer, 229
Physisorption, 229-231
Physisorption and desorption of nonsolvent molecules, 231
Pianka, Eric R., 176
Pick-and-place, 27, 56, 130, 138, 144, 150, 151
Picornavirus, 104
Pig, 219
Pineda, Valenti, xx, 85-87, 184
Pioneer, 35
Pipeline, 36, 138, 192, 194
Piracy, 197
PIRAIA Project, 34
Pister, Kristofer, 58, 116
Piston fluid flow dynamics, 225, 227-231
Piston operation in the desorption and viscous regimes, 229-231
Piston plate, 134, 135, 223, 224, 226, 227, 229-231
Piston rod, 134, 223, 226, 227
Piston spring, 134, 226, 227
Piston throw, 223, 227, 228
PITAC, xvii, 28
Pixelbots, 35
Planarian, 167
Plasma cell replicator, 81
Plasmid, 104, 105, 110, 166, 168
Plastic Lucite block, 207
Plastic replicator, 65
Plastikant, 35
PlayMobile, 35
Plekhanov, A.D., 180
PNA, 112
POE model of bio-inspired hardware systems, 146, 149
Point mutation, 169, 172, 173
Poiseuille's Law, 227
Polar body, 107
Pole preference, 104
Poliomyelitis, 102, 110, 156, 208
Pollack, Jordan, xx, 14, 64-67, 69, 78
Polyautomata, 11
Polybot, 31, 32
Polyketide synthases, 101
Polymerase, 6, 92, 93, 96-98, 100, 102-104, 107, 109, 110, 112, 113, 197
Polymer mechatronics, 65
Polymorphic robots, 58
Polynomial population growth, 188-191
Polynucleic acid structures, 58
Polynucleotide, 57, 58, 96, 110
Polypod, 31
Polytype electromechanical replicator, 60
Polyyne, 126, 133
Population ecology, 190, 191
Population ecology of machine replicators, 191
Population entropy, 190
Population invasions and diffusion models, 190
Porphyrin, 91, 95
Positional accuracy, 166, 213
Positional assembly (cf. self-assembly), 90
Positional assembly, xvii, 55, 58, 89, 90, 96, 100-102, 109-115, 117, 133, 137, 152, 166, 182, 184, 211-213
Positional assembly using DNA, 110-112
Positional assembly using microbes and viruses, 114, 115
Positional assembly using proteins, 112-114
Positional atomic-scale mechanosynthesis, 208
Positional control, 90, 112, 125, 213
Positionally controlled chemical synthesis, 135
Positional mechanochemistry, 125
Positional nanoparts assembly, 112
Positional parts assembly, 110
Positional uncertainty, 130, 213, 224, 233
Positioning accuracy, 125
Positioning devices, 125
Positioning motions, 125
Pospichal, Jiri, 119
Potato spindle tuber viroid, 102
Potential design errors, 204, 210, 211

Pournelle, Jerry, 43
Poverty and hunger, 196
Power law, 174-176, 185, 188, 193
Power law scaling in convergent assembly nanofactory systems, 193
Power scaling law, 192, 193
Poxvirus, 104
Precision Micro Assembly Laboratory, 117
Predator-prey interactions, 190
Pregnancy, 167, 186-188
Premanufactured parts, 162
Pre-nanotechnology macroscale replicators, 175
Prenatal-active replicators, 187, 188
Prepattern, 163
Press, Joseph Henry, 199
Pressure-threshold actuator, 128, 129
Price, Charles, 108
Prices of nanoscale-structured products, 203
Primase, 104
Primus Engineering Outfits, 35
Princeton University, 5
Print houses, 65
Printing large buildings, 65
Prion, 11, 23, 100, 101, 113, 148, 156, 172, 199
Private experimentation in explosives and rocketry, 205
pRNA, 111
Probabilistic model, 6
Probe array, 57, 67, 183
Process accounting, 169
Process energy autonomy, 164
Process energy centralization, 164
Process energy efficiency, 164, 165
Process energy redundancy, 164
Process energy storage, 164
Process energy types, 164
Process functionality of active subunits, 164
Processive, 148, 168
Process manipulation autonomy, 165
Process manipulation centralization, 165
Process manipulation closure, 170
Process manipulation redundancy, 165
Process materials storage, 160
Process security, 169
Producer, 27, 63, 147, 173
Product assembly time, 192
Product boundary, 171
Product design, 25, 28, 141
Product export through boundary, 160
Production amplification, 63
Production bottlenecks, 170
Production facility, 3, 36, 46, 47, 51, 64, 76
Production lines vs. Replicators, 195
Production module, 141-143
Production parts depot, 47
Production phase, 121
Production planning, 25
Production rate, 52, 187, 192
Productive nonreplicators, 152
Productive replicators, 15, 152
Product mass, 171, 172, 181, 182
Product naturalicity, 171
Product particity, 172
Product physical dimensionality, 171
Product physicality, 171
Product retrieval system, 47, 48
Product scale, 171, 178
Products already manufactured by replicators, 202, 203
Products depot, 47
Product size, 171, 192
Product structural error rate, 172
Product structural fixity, 171
Product structure, 124, 128, 141, 153, 168, 171, 172
Product technology level or granularity, 171
Programmability and learning, 174
Programmable, xvii, 13, 25, 29, 30, 35, 41, 54, 57, 76, 80, 95-97, 108, 118, 135, 141, 159, 165, 166, 194, 195, 201, 204, 206, 207, 209, 212, 213, 217
Programmable Artificial Cell Evolution (PACE) project, 108
Programmable assembly, 54, 165
Programmable catalyst, 119
Programmable material, 57
Programmable matter, 29, 159
Programmable microbes, 207
Programmable Molecular Positional Assembly, 212, 213
Programmable nanoscale assembler, 97
Programmable operations, 165, 166
Programmable self-assembly, 95
Programmable surfaces, 30
Programmed DNA deletion, 172
Project Daedalus, 38, 39
Prokaryote, 79, 97, 101, 103-105, 107, 157, 160
Proliferation, 44, 78, 180, 197
Prometaphase, 106
Proofreading, 110
Prophage, 103
Prophase, 105
Protein-based molecular motors, 113
Protein-directed parts assembly, 113
Protein Programming™, 108
Protein stitchery, 111
Proteosome, 113
Proto-DNA, 150
ProtoLife, 108
Proton beam nanolithography, 118
Protopterus aethiopicus, 156
Prototype assemblers, 135
Prototype microscale assemblers, 139, 144, 184
Prototype nanoscale assemblers, 140, 144, 184
PrP, 100, 101, 156
Prusiner, Stanley B., 101
Pseudocrystalline self-assembly, 95
Pseudomonas pyocyanea, 221
Pseudomonas stutzeri, 114
Pseudorotaxanes, 93
Psittacosis, 102
Psycho-robotics, 20
Public safety, 10, 14, 35, 145, 146, 154, 162, 169, 170, 172, 176, 196-199
Pulsers, 9
PUMA, 45, 46, 179
Pyrenomas salina, 156
Pyrolysis of acetylene, 226, 227, 232
Pyrotechnics, 206

Q

Quadro, 35
Quaking aspen, 219
Qualitative/quantitative closure, 170, 171
Quantum dot, 90, 113, 115, 171, 198
Quantum mechanical automata, 118

Quantum uncertainty, 207
Quate, C.F., 183
Queen Christina of Sweden, 1
Quest for Self-Replicating Systems, 37
Quines, 12

R

R3C ligase ribozyme, 96, 221
Rabbit, 113, 184-188, 220
Rabbit formula, 186, 188
Rabies, 102
Raccoon, 220
Radcliffe, Edward B., 190
Radio-controlled bacteria, 114
Radio robot, 33
Railgun, 17, 78
Randall, John N., xx
Random bin-picking, 94
Random Morphology Robot Project, 34
Rapid laser prototyping, 67
Rapid prototyping, 35, 38, 64, 65, 67, 116, 175
Rare nutrients, 169
Rasmussen, Steen, 29, 96, 110, 178, 206
Rat, 220
Ratchet, 21, 100, 113, 128-130, 134, 155, 156, 178, 211
Rattlesnakes lacking rattles, 172
Ray, Thomas S., xvii, xx, 12, 13, 156
RCA, xxi
Reaction-diffusion systems, 155
Reaction-diffusion type replication, 95
Reaction networks, 150, 154
Reactive encounter mechanisms, 124
Read-only memory, 174
Rebek, Julius, Jr., 96, 97, 156
Recipe, 10, 155, 179
Reconfigurability, 63
Reconfigurable, 18, 29, 30, 32, 33, 79, 81, 194, 195
Reconfigurable computing, 195
Reconfigurable modular manipulator system, 33
Recursion theory, 2
Red alder, 219
Reddy, Raj, xvii, 28, 37, 227
Red fox, 220
Redl, Franz X., 93
Redundancy, 6, 41, 110, 141, 153, 155, 164, 165, 173
Reed College, xix, 108
Refloration bacteria, 203
Regeneration, 145, 148, 149, 175
Regeneration time, 175
Reggia, James A., xx, 11, 12, 29, 146, 147, 169, 170, 179
Regis, Ed, 116
Registry of Standard Biological Parts, 114
Regulation, 93, 109, 146, 154, 196-198, 206, 226
Reif, J.H., 92, 112
Relative position, 163
Reliability, 6, 41, 63, 119, 127, 130, 131, 158, 164, 165, 169, 207, 214
Reliability during operation, 214, 215
Reliability of manufacturing operations, 169
Relinquish, 162, 205
Remote-control, 17, 69, 73, 76, 114, 133, 154, 184
Remote-controlled enzymes, 114
Remote-controlled self-replicating robots, 69, 76
Remote powered, 164
Rensselaer Polytechnic Institute, xix, 33, 117, 140, 144
Reovirus, 104
Repairable robots, 67, 68
Replicase, 109, 177, 179, 180
Replicating assemblers, 119, 146, 147, 204, 208
Replicating brick, 125-130
Replicating loop, 12, 29
Replicating string, 82, 83, 85
Replicating swarm, 30, 31
Replicating systems, xvii, xix, 4, 11, 17, 23, 25, 28, 35-42, 44, 53-55, 63, 64, 68, 69, 75, 76, 78-80, 82, 83, 91, 95, 96, 98, 110, 111, 118, 120, 130, 132, 145, 146, 148, 150, 151, 153, 155, 156, 168, 172, 173, 175, 176, 179, 180, 182, 184, 185, 188-190, 194, 196-199, 201, 204, 205, 207, 208, 212, 213, 215, 216, 219
Replicating Systems Concepts (Team), 44, 120
Replicating water plants, 25
Replication (cf. self-replication), 89, 90
Replication auxeticity, 167, 195
Replication by component analysis, 16
Replication by proxy, 2
Replication by self-inspection, 17
Replication control, 17, 153, 154, 170
Replication control abstractivity, 153
Replication control autonomy, 153, 170
Replication control centralization, 153
Replication control complexity, 153, 154
Replication control maintenance, 154
Replication-control mechanisms, 172
Replication control redundancy, 153
Replication control source, 153
Replication cycle, 7, 22, 24, 85, 104, 121, 126, 127, 132, 133, 168-170, 172, 175, 185-188, 214, 224, 226, 233
Replication data self-policing, 172
Replication fidelity, 169, 172, 173
Replication fork, 104
Replication goal specialization, 167
Replication-incompetent viruses, 170
Replication informatic energy ratio, 165
Replication information, 153-157
Replication information abstractivity, 155
Replication information autonomy, 154, 155
Replication information context tolerance, 157, 158
Replication information sharing, 156
Replication information type, 155
Replication is nothing new, 199
Replication parts depot, 47
Replication process, 11, 13, 14, 41, 72, 75, 78, 79, 83, 151, 153, 154, 158-160, 163, 166-168, 191, 194, 195
Replication process centralization, 166, 191, 195
Replication process digitality, 168
Replication process intermediaries, 167
Replication process parallelicity, 168, 195
Replication process specialization, 166, 167, 191, 195
Replication process subunit assistance, 167, 195
Replication process timing, 167
Replication speed, 4, 175, 176
Replication substrate, 153, 158
Replication substrate phase, 158
Replication substrate temperature, 158
Replication time, 51, 52, 99, 102, 138, 141, 145, 164, 169, 170, 174-179, 186-189, 192-195, 219-221, 224, 225
Replication time vs. replicator mass, 175, 176
Reproduction vs. replication, 4, 89
Replication without description, 16, 17

Replicative capacity, 170, 179, 180
Replicative energy commitment, 165
Replicative influence, 166
Replicator, xvii, 1, 2, 4, 6-8, 10, 12, 13, 15, 17, 19, 21-25, 28-30, 34, 35, 37, 38, 44-46, 52, 53, 55, 58-60, 63, 65, 69-78, 80, 81, 85, 87, 89, 90, 96, 101, 106-110, 117-121, 136-140, 145-149, 152-176, 178-182, 184-191, 193-199, 201, 203-208, 212, 215, 219-221
Replicator activity/passivity, 166
Replicator boundary, 160, 168
Replicator computer, 161
Replicator contiguity, 161
Replicator description alphabet, 156, 157
Replicator description size, 155, 156
Replicator design space, 4, 55, 89, 145, 146, 152, 153, 167, 176, 185, 195
Replicator energetics, 153, 164
Replicator expiration date, 169, 170
Replicator information centralization, 155
Replicator information lockout, 156
Replicator information redundancy, 155
Replicator kinematics, 153, 165
Replicator lifespan, 188
Replicator longevity, 169
Replicator manipulation degrees of freedom, 165
Replicator mass, 145, 160, 174-176, 178, 219-221
Replicator naturalicity, 159
Replicator networks, 148
Replicator nutritional complexity, 162
Replicator parasiticity, 166
Replicator parentage, 167
Replicator particity, 160
Replicator parts synthesis, 168
Replicator pattern instantiation specificity, 157
Replicator performance, 152, 153, 169
Replicator physical dimensionality, 159, 160
Replicator physicality, 158, 159
Replicators and artificial intelligence, 145, 195, 196
Replicators and public safety, 145, 196-199
Replicator scale, 160
Replicators can be made inherently safe, 199
Replicator size, 4, 89, 175, 176
Replicator structural fixity, 160
Replicator structure, 146, 148, 153, 159, 161, 167, 180
Replicator taxonomy, 146
Replicator technology level or granularity, 159
Replicator triviality or complexity, 157
Replicon, 102, 105
Repressilator, 114
Reproducer, 4, 146, 150, 151, 157, 170, 176
Reproduction, xix, 2, 4, 6, 10, 11, 15-18, 20, 26, 37, 40, 44, 54, 55, 68, 69, 89, 103, 107, 115, 117, 145, 148-150, 155, 157, 159, 165, 167, 172-176, 180, 181, 185, 189-191, 219
Reproduction vs. replication, 4, 89
Reproductive maturity, 170, 176
Reproductive mechanics, 54
Reproductive power, 176
Reproductive strategy, 190
Requicha, Aristides, xx, 89, 162
Required parts preparation, 162
Residential house, 203
Resnick, Mitchel, 34
Resonance, 182, 183, 225-227, 232, 234
Respirocyte, 164, 195
Restricted evolution, 155
Restriction to hydrocarbon materials, 213, 214
Retractile cascade, 12
Retrovirus, 102, 104
Reverse engineering, 3, 16, 155
Reverse transcriptase, 174
Reversible cellular automata, 12
Reversible computer, 12
Reversible mutations, 173
Rewritable memory, 174
Reynolds, Glenn, 198, 205, 228
Reynolds number, 228, 231
Rhabdovirus, 104
Rhesus monkey, 220
Rhinovirus, 102
Rhomblocks, 35
Ribonucleoprotein, 97
Ribonucleoprotein machine, 97
Ribosome, 6, 15, 96-102, 104, 106, 107, 110, 113, 119-121, 133, 153, 156, 165, 169, 177-179, 182, 207, 211, 212, 219, 221
Ribosome molecular assembler, 100
Ribozyme, 96, 97, 102, 103, 109, 110, 112, 113, 177, 221
Rice University, xix
Richter's Anchor Blocks, 35
Rickettsia, 172
Riehn, Robert, 66
Riek, Roland, xx, 101
RISC, 161
Risk assessments for nanotechnology, 198
Risk management, 197
Risk paradigms, 198
Risner, Jeremy, 66
Rivera, Omar, 72
River Rouge complex, 180
RMMS, 33
RNA, 82, 92, 96, 97, 100-105, 107, 109-113, 156, 157, 160, 162, 174, 177, 179, 180, 182, 211
RNA-dependent RNA polymerase, 102, 110
RNA polymerase, 98, 100, 102, 103, 107, 109, 110, 112, 113
RNA replicase, 109
Robiobotics LLC, 108
Robobiologics, 2
Robocasting, 66
Robosphere, 81
Robot birth factory, 159
Robot colony, 67
Robot factory, 3, 26, 27, 37, 75, 167, 169, 184, 208
Robotically-constructed robots, 67
Robotic assembly, 28, 81
Robotic deposition, 66
Robotic ecologies, 80, 81
Robotic fabrication, 81
Robotic genome, 63
Robotics and Intelligent Machines Laboratory, 117
Robotics Institute, xvii, xix, 28, 34, 117
Robotic society, 63
Robotix, 35
Robot Jurassic Park, 35
Robot Kinematics and Motion Planning Lab, 32
Robot replication, 45, 46, 152
Robot reproduction, 159
Robots capable of mutual repair, 68
Robot self-replication, 45
Robots On Your Doorstep, 20
Robozymes, 112, 141
Rocha, Luis M., 156, 157
Rock hyrax (*Hetero. b*), 220
Rock hyrax (*Procavia hab*), 220
Roe deer, 220
Rohrer, Heinrich, 202

Rokenbok, 35
Rolling circle replication, 102, 110
Rosen, Charles, 45
Rosette nanotube, 91, 93
Rossler, O., 96
Rossum's Universal Robot (R.U.R.), 2, 169
Rotapod™, 55, 138-141, 184
Rotary assembler, 136
Rotaxane, 91, 93, 113
Rothemund, Paul W.K., 95
Rowland Institute, 114
RP, 64
rRNA, 97, 98, 99, 100, 107
RSC Team, 44, 45, 46, 49, 76
r-selection, 190
R.U.R., 2, 169
Russell, Jeffrey D., 182
Rutgers University, xix, 65

S

Saberhagen, Fred, 38
Saccharomyces cerevisiae, 109, 156
Sadin, Stanley, 42
Safe designs, 197
Safeguard, 15, 161, 170, 196, 197, 199
Safe nanotechnology, 198
Safe procedures and methods, 197
Safe replication, 11, 17, 18, 196
Safe replicator designs, 174
Safety, 4, 10, 14, 15, 30, 35, 107, 108, 145, 146, 153, 154, 161, 162, 169, 170, 172, 174, 176, 178, 179, 196-199, 204, 205, 213
Safe version, 206
Sagan, Carl, 38, 42, 195
Sagan Study Group, 42
Saitou, Kazuhiro, xx, 23, 94, 95
Salamander, 174
Salivarex™, 199
Salk Institute, 95
Sallows, Lee, 180
Sallowsgrams, 180
Salmonella typhimurium, 109
Salmonella typhosa, 221
Sanchez, E., 4
Sanderson, Arthur C., xx
Sandia National Laboratories, 66, 117
San Diego State University, xix
Sanduloviciu, Mircea, 81, 82
San Jose State University, xix
Santa Claus machine, 37, 38
Santa Fe Institute, xix
Saprophytic life, 155
SARS coronovirus, 156
Sayama, Hiroki, xvii, xix, xx, 12, 157, 158, 167, 171
Scaffold for functional devices, 111
Scaffolds for nanomaterials synthesis, 115
Scalability, 224
Scanning-probe array, 57
Schefflers, 35
Schneiker, Conrad, 108
Schultz, Peter G., 109
Schuster, P., 96, 172
Schwarzschild radius, 178
Science/AAAS, xx, 4
Science fiction, 2, 12, 19, 25, 30, 38, 43, 44, 82, 195
Science Network, 28
Scientific American, 7, 19, 103
SciNet, 28
Sciperio Inc., 67
Scire, F., 202
Scrapie, 100, 101
Scripps Institute of Oceanography, 42
Scripps Research Institute, 93
Script kiddies, 204, 205
Sealed laboratory, 197, 198
Seed, 11, 14, 15, 17, 19, 21, 23, 36, 38-40, 49, 51, 59, 60, 79, 107, 138, 150, 154, 166, 175, 194
Seed lethality gene, 154
Seek broad attractors in the design space, 215
Seeman, Nadrian C., xx, 57, 58, 92, 96, 110, 111, 182
Segre, Daniel, 163
Selective laser sintering, 64
Self- (clarified), 89, 90
Self-alignment, 168
Self-assembled DNA, 92, 93
Self-assembled electronic circuit patterns, 111
Self-assembled fluorescent conformational switch, 94
Self-assembling automaton, 95
Self-assembling catenanes, 94
Self-sssembling crystalline solids, 91, 93
Self-assembling dendrimers, 91, 93
Self-assembling lipidic micelles, 90
Self-assembling molecular machine structures, 91
Self-assembling monolayers, 90, 151
Self-assembling nanodevices, 199
Self-assembling peptide, 91
Self-assembling rotaxanes, 91, 93, 94
Self-assembling tectoRNA, 112
Self-assembling thin films, 90
Self-assembling 3-D metamaterial, 93
Self-assembling triangular parts, 95
Self-assembly (cf. positional assembly), 90
Self-assembly, xvii, 1, 23, 29, 31-33, 35, 56, 58-60, 69, 89-95, 100, 102, 103, 109-113, 115, 119, 137, 148, 151-153, 166, 182, 184, 191, 198, 212
Self-assembly of block copolymers, 93
Self-assembly of carbon nanotube, 111
Self-assembly of mechanical parts, 91, 94, 95
Self-assembly of molecular parts, 93
Self-assembly of parts, 94
Self-assembly of proteins, 110
Self-assisted assembly, 137
Self-clocking, 83
Self-complementarity, 96
Self-destruct, 105, 169, 172
Self-excising error-correcting code, 110
Self-extending machines, 78
Self-formation, 28, 168
Self-formation modality, 168
Self-inspection, 16, 17, 155
Self-ligating polynucleotide systems, 96
Self-maintaining, 145
Self-movable robot, 58
Self-organization, 14, 31, 81, 82, 163, 182
Self-organizing maps, 163
Self-organizing nanostructures, 90
Self-policing modifiers, 174
Self-pollination, 154
Self-reconfigurable, 32, 33
Self-reconfiguring robots, 34, 81
Self-reference, 6, 16
Self-referential, 3, 13, 180
Self-referential pangram, 181
Self-regulation, 197, 198

Self-repairing, 10, 13, 19, 29, 30, 33, 35, 37, 67, 81, 145, 149
Self-repairing machine, 29
Self-repairing robot, 67
Self-replicability, 159, 179
Self-replicating automata, 5, 13, 42
Self-replicating automated industrial factory, 25
Self-replicating chemical systems, 179
Self-replicating circuits, 79
Self-replicating computer program, 12, 14, 207
Self-replicating construction machine, 60-63
Self-replicating factory, 17, 19, 25, 42, 46, 76, 104, 152, 184, 188, 189, 193, 199
Self-replicating interstellar probe, 38, 39, 189-191, 219
Self-replicating LEGO®, 69-75
Self-replicating loops, 12, 29
Self-replicating lunar factory, 36, 46, 51, 76-79, 156, 180, 184, 219
Self-replicating machines, xvii, xix, 1, 4-8, 10, 19, 21, 23, 34, 38, 40, 41, 44, 53-55, 69, 78, 90, 98, 109, 145, 158, 161, 172, 178-180, 184, 197, 205
Self-replicating manufacturing stations, 55, 139
Self-replicating molecular machines, 96
Self-replicating molecular strands, 119
Self-replicating molecular system, 11, 96
Self-replicating molecule, 12, 96, 101, 146, 147
Self-replicating pattern, 15
Self-replicating peptide, 96
Self-replicating physical polymers, 95
Self-replicating physicochemical system, 110
Self-replicating plasma balls, 82
Self-replicating program, 12, 41
Self-replicating protein misfold, 172
Self-replicating PUMA robot, 179
Self-replicating robots, xvii, xix, 3, 14, 16, 19, 20, 26, 28, 42, 44, 45, 63, 69, 73, 75, 76, 78, 79, 81, 85, 127, 146, 150, 151, 172, 208
Self-replicating robotic factory, 76, 78
Self-replicating robotic lunar factory (SRRLF), 85-87
Self-replicating software, 1, 12
Self-replicating spots and pulses, 95
Self-replicating stars, 82
Self-replicating string, 82
Self-replicating system, xvii, 4, 23, 25, 28, 35, 36, 37, 40-42, 44, 54, 63, 64, 69, 75, 76, 78-80, 82, 91, 95, 96, 98, 110, 111, 130, 145, 151, 155, 156, 172, 173, 175, 176, 180, 184, 185, 188, 189, 194, 196-199, 201, 204, 205, 213, 216
Self-replicating telefactors, 43
Self-replicating wire, 82, 84, 85
Self-replication (cf. replication), 89, 90
Self-replication (cf. self-reproduction), 4, 89
Self-replication, xvii, xviii, xix, 1-4, 6, 10-14, 16-19, 21, 27, 29, 30, 34-39, 41, 42, 44-46, 48, 51, 60, 63-65, 67, 69, 70, 75-79, 81, 82, 85, 89-91, 95, 96, 99-101, 104, 107, 111, 117, 119, 121, 122, 125, 132, 133, 136, 145, 146, 149, 151, 158, 159, 164, 166, 167, 169-171, 173, 175, 178-181, 184-186, 188-190, 198, 199, 204, 205, 207, 208, 212, 213, 215
Self-Replication Contest, 19
Self-replication in chemistry, 95
Self-replication in molecular manufacturing, 213
Self-reproducing computer program, 13
Self-reproducing lipid vesicles, 148
Self-reproducing machine, 3, 6, 11, 19, 20, 23, 35, 38, 40, 67, 196
Self-reproducing robots, 2, 20, 37, 68
Self-reproducing society, 157
Self-reproducing system, 25, 156, 157, 171
Self-reproduction (cf. self-replication), 4, 89, 90
Self-reproduction, xix, 2, 4, 10, 11, 17, 26, 68, 89, 107, 117, 145, 148, 150, 157, 173, 180, 181
Self-splicing, 110
Self-sufficient, 28, 40, 166, 204
Self-sustaining, 4, 67, 68, 80, 81
Self-sustaining robotic ecologies, 80, 81
Self-test for base pair mutations, 173
Semantic closure, 155, 182
Semi-autonomous, 153
Semi-autonomous self-replicating robot, 75
Semiconductor, xxi, 27, 35, 37, 66, 90, 93, 113, 135, 136, 182
Senzyme, 115
Sequeira, Eldrid, 114
Sequence-dependent devices, 111
Sequential random bin-picking, 95
Sequential semi-auxetic replication, 167
Serial microassembly, 150
Serial processing, 168
Serratia marcescens, 114
SETI, 38
Seuss, Dr. (Theodor Seuss Geisel), 114
Sex, 107, 161, 172
Sexual reproduction, 4, 149, 157, 167, 172, 174
SFF, 52, 64, 66
Shape-changing robots, 58
Shape-selective self-assembly, 95
Sheathed loops, 11
Sheep, 203, 220
Shi, J., 110
Shigella dysenteriae, 221
Shih, W.M., 92
Shinto ritual, 27
Shoch, John F., 12
Shock wave formation, 232
Shoulders, K.R., 37, 52, 117
Shoulders electronic micromachining replicator, 117
ShowFlow, 184
Shu, D., 111
Shultze, 115
Sigmund, K., 96
Silcox, Peter, xx, 17
Silicon origami, 95
Silicon Scribe, 55
Silk, 203
Silkworms, 203
Silver, 39, 66, 75, 93, 111, 113, 114
Silver nanowire arrays, 93
SimCAD, 184
SIMD architecture, 133
Simmons, Kim H., 186
Simon, Herbert A., 191
Singh, Push, 196
Single-band operation, 227, 228, 231
Single-biopolymer system, 177
Single-robot-without-fixture replication, 151
Sipper, Moshe, xx, 4, 19, 29, 148, 149
Sipper POE model of bio-inspired hardware systems, 149
Sipser, Michael, xx
Site-specific DNA, 111
Size Limits of Very Small Microorganisms, 176
Size of kinematic replicators, 145, 176-178
Skidmore, George, 17
Sladek, John Thomas, 179
Slayden, Cameron, xx, 4
Slime molds, 167
Slow loris, 220
SLS, 64
Smallest molecule capable of replicating itself, 179
Smalley, Richard E., 203, 207, 214, 223

Smart, John, xx
Smart dust, 116
Smay, James E., 66
Smith, Alvy Ray, 11
Smith, Arnold, 14
Smith, Bruce, 111
Smith, David B.S., 193
Smith, Hamilton O., 108, 111
Smith, John Maynard, 4, 10, 148, 172
Smith, J.S., 95
Smith, Steven S., xx, 92, 94, 110, 112-114
Snare, Andrew J., 119
Snowshoe hare, 190, 191
Societal Implications of Nanoscience and Nanotechnology, 198
Socioeconomic impact of machine replicators, 199
Socio-robotics, 20
Software simulators for robots and automated manufacturing, 184, 185
Software viruses, 205
Soka University, xix
Solarbot, 33
Solar canopy, 49, 51
Solar cell, 42, 49, 53, 64, 79, 85, 181, 204
Solar energy, 25, 37, 41, 44, 48, 49, 53, 63, 77, 78
Solar power satellite, 36, 42
Solid freeform fabrication, 38, 52, 64, 66
Solid printing, 64-67, 175
SolidWorks, 184
Solitary replication, 148
Sommerfeld, William, 12, 156
Sonolytic pyrolysis, 226, 227
Sorcerer's Apprentice, 154, 155
Sorensen, Mark, 72
Sosic, Rok, 159
South Bank University, xix
Space colonies, 36, 37
Space Hardware Optimization Technology (SHOT), Inc., 79
Space Manufacturing Conference, 45
Space manufacturing systems, 35-37
Space shuttle, 30, 42
Space solar power, 63, 64
Space Studies Board, 176
Space Studies Institute, xviii, 36
Spalding, Charles H., 46
Sparrow, 220
Spatial dispersal patterns, 190
Specialization, 81, 140, 141, 149, 166, 167, 184, 185, 191, 194, 195
Specialized factory, 194
Specialized replicating system, 194
Special transmission states, 8
Specific design guidelines, 197
Specific energy for replication, 164
Specific identity, 163
Specificity of the design, 216
Speed of light, 178, 189
S phase, 105
Spiders, 32, 220
Spiegelman, Sol, 102, 179
Spliceosome, 113
Sponges, 115
Spores, 79, 167
Springer, George S., 226
Sprout-Waldron Company, 40
Square-Cube law, 224
SRI International, 43
SRMS, 55
SRRLF, 85, 86, 87
SRS, xvii, 44, 51, 79, 80, 175, 189
SSI, 36, 37, 45
SSP, 63
Stabil, 35
Stable cavitation, 232
Stadler, P.F., 96
Stanford Research Institute, 45
Stanford University, xix, 120
Stanford University course (CS 404), 120
Stanlo, 35
Staphylococcus aureus, 221
Star Trek, 38, 187
Star Wars, 3
Stassinopoulos, D., 96
Steelbuilder, 35
Steel Engineering, 35
Steel Tec, 35
Stemniski, Paul, 73
Stentor coeruleus (Ciliata), 220
Stereogenic, 91
Stereolithography, 35, 52, 55, 64, 65, 67, 117
Sterling, Bruce, 209
Stewart, Ian, 4
Stewart platform, 126, 128-130, 132, 134, 213, 223, 233, 234
Stewart platform manipulator, 128, 132, 134, 223, 234
Sticky fingers, 206, 207
Stiction, 211
Stigmergy, 182
Stirling engine, 79
STM, 117, 136, 183, 202, 203, 207, 212
Stochastic parallel microassembly, 151
Stockroom, 6, 7
Stoddart, Fraser, 93, 94
Stokes' law, 228, 231
Stokes' law drag power, 228, 231
Stokes sedimentation law, 224
Stokys, 35
Storage-based systems, 149, 154
Strandh, Sigvar, xx, 1
Stratasys Inc., 64
Strategies for exponential kinematic self-replication, 186-188
Streptococcus lactis, 221
Strict replication fidelity, 172
Stride, Scot L., xx
Structo, 35
Structomode, 35
Structural information, 155
Structure-replicators, 157
Study On Safe Nanotechnology, 198
Stuke, M., 67
Sturgeon, William, 209
Sub-exponential growth, 190
Substrate naturalicity, 158
Substrate physical dimensionality, 158
Substrate physicality, 158, 159
Substrate sufficiency, 158
Substrate technology level or granularity, 158
Subtractive mechanosynthesis, 168
Subtractive synthesis, 168
Subunit, 3, 85, 91, 93, 96-99, 102, 140, 153, 155, 160, 163-167, 169, 171, 174, 179, 186, 194, 195
Subunit fate, 163
Subunits presentation, 163, 164
Subunit targeting, 163
Sugawara, H., 176
Sugita, Motoyosi, 101
Suh, J.W., 183
Suh, N.P., 61, 181

Sun, Hong-Bo, xx, 66
Superautomation, 26
Supergiant stars, 4
Supporter, 42, 147, 197
Suppressing evolvability, 172
Suppressor gene, 154
Suppress variability, 172
Supramolecular tetrahedra, 112
Survivability, 179, 188
Sussman, Gerald J., 114
Suthakorn, Jackrit, xx, 17, 44, 69-77, 151, 152, 158
Suthakorn-Chirikjian categorization of self-replicating robots, 146, 151, 152
Suthakorn-Chirikjian LEGO® replicator, 176, 220
Suthakorn-Cushing-Chirikjian autonomous replicator, 75-77, 208
Swarm, 29-34, 76, 81, 166, 182
Swarm-bots Project, 33
Swarm construction, 166
Swarm robotics, 34
Swedish Institute of Computer Science, xix, 34
Sweet birch, 219
Swiss Federal Institute of Technology, xix, 13
Symbiont, 101, 166
Symbioorganism, 12, 150, 160
Symbiosis, 101
Symmetric MultiProcessors, 182
Synthase, 101, 177
Synthetic amino acids, 113
Synthetic Biology Lab, 109, 110, 114
Synthetic cell biology, 109
Synthetic enzymes, 113
Synthetic lifeforms, 109
Synthetic organisms, 109
Synthetic polio RNA, 110
Synthetic RNA, 110
Synthetic viroid, 110
Syracuse University, xix
System assemblers, 122, 136
Systematic closure engineering, 180
System closure, 182
System information content, 164
Szathmary, Eors, 4, 148-150, 154, 163, 170, 172, 190
Szathmary classification of replicators, 146, 148, 149
Szostak, Jack W., 109

T

2001, 38
2010, 38
T-1000, 30
T4, 102, 103, 156, 221, 228
T7, 110
3-D electromechanical components, 65
3-D electronic components, 65
3-D gadget printer, 66
3-D microstructures, 67
3-D nanostructure fabrication, 67
3-D printer, 64, 65
3-D resin-sculpted bull, 67
3-D solid printing, 64, 66
3D Studio Max, 184
3D Systems, 64, 66
3-D tubes of living tissue, 67
Tabletop-sized factories, 116
Takno, 35
A Tale of Two Cities, 116
Tamper resistance, 169
Tan, Weihong, 111
Taneja, Vidya S., 186, 189
Tang, Jon, 74
TAPET, 109
Tapeworms, 118, 119, 166
Taxonomy of replicators, 145
Taxonomy of risk assessments for nanotechnology, 198
Taxonomy of taxonomies, 146
Taylor, Theodore B., xx, 37, 38, 52, 117
Taylor Santa Claus Machine, 37, 38
Taylor, Tim, 10, 150, 151
Taylor categorization of reproducers, 146, 150, 151
TECC, 35
Technische Universitat Ilmenau, xix
Technology level, 158, 159, 171
TectoRNA, 96, 112
Teeth, 61, 167
Teknik, 35
Tektology, 145
Teleautonomy, 63, 133
Telecube, 32
Telefactor, 40, 42, 43, 63
Telefactors Working Group, 42, 63
Teleoperated kinematic replicator, 70-74
Teleoperated microassembly, 150
Teleoperated replicators, 46, 170, 178
Teleoperation, xviii, 17, 31, 32, 36, 40, 42, 43, 45, 46, 49, 51, 63, 69-74, 115, 132, 133, 150, 153, 154, 158, 164, 170, 175, 178, 180, 181
Teleoperation-management system, 51, 132
Telepresence, 36, 40, 133
Telerobotics, 133
Telomeres, 169, 170
Telophase, 106
Temin, H.M., 174
Tempesti, Gianluca, xx, 6
Template, 8, 15, 17, 40, 55, 56, 67, 82, 91-93, 95, 96, 101, 108-111, 113, 115, 146, 148, 155, 157, 162, 179, 183, 198, 210, 226, 233
Template-based reproduction, 155
Template-dependent ligation, 91
Template-directed colloidal crystallization, 93
Templated self-assembly, 93
Templated synthesis of porphyrin systems, 91
Template molecules, 91, 157
Temporal dimensionality, 159
TemSi, 35
Tenrec, 220
Termination dates, 197
Terminator 2, 30
Terminator technology, 154
Termite, 166
Terraforming, 24, 25, 79
Territory formation, 35, 190
Tessellation, 8, 11, 29
Tessellation automata, 11
Testes, 167
Tethya aurantia, 115
Tetrahymena, 107, 172
Tetrahymena pyriformis, 107
Tetrobot, 33
Thale Stahlbau Technik, 35
Thallus, 101
Thatcher, James, 15, 16
Thatcher's Variant, 15, 16

The Cat in the Hat Comes Back, 115
The Constructioneer, 35
The Engineer, 35
The Lover of Lies, 155
The Magician's Assistant, 155
The Preparation, 86, 87
The Reproductive System, 179
Therics, 67
Thermal expansion, 225, 232
Thermal expansion in diamond walls, 232
Thermal noise, 130, 206, 207, 213, 227, 233
Thermal vibrations, 119, 122, 164, 211
Thermite, 169
Thermojet solid object printer, 66
ThermoJet 3-D printer, 64
Thermostat, 154
The Selfish Gene, 146
The Sentinel, 38
The Shockwave Rider, 12
The Sorcerer's Apprentice, 154, 155
Thimbleby, Harold, 12
Thiomargarita namibiensis, 103
Third World, 196
Thompson, Clive, 205
Thompson, Richard, 29
Thorson, Mark, 30
Throughput closure, 180, 181, 192
Thymidine synthesis, 161
Thymine dimer bypass, 110
Tibetan, 116
Tierra, 12, 13, 150, 156, 157
Tierran organisms, 150
Tilden, Mark W., xx, 2, 29, 35, 146-148, 172
Time of fecundity, 175
Timing of subunit activation, 164
Tinkertoys®, 35
Tipler, Frank J., 38
tmRNA, 100
TMV, 102
Tobacco mosaic virus, 102
Tobacco ringspot virus, 102
Todd, Paul, 79
Todd Robotic Lunar Ecopoiesis, 79
Todo, Isao, 29
Toffoli, Tommaso, 29
Togavirus, 104
Tohoku University, xix
Tomassino, Marco, xx
Tom Thumb algorithm, 12
Toobers & Zots, 35
Tool chuck, 134, 223
Top-down, 108, 115, 116, 144
Total automation, 26, 27
Toth-Fejel, Tihamer, xx, 26, 29, 30, 35, 79-81
Toth-Fejel kinematic cellular automata, 79
Toxicology risks, 206
Toyota Motor Corp, 116
ToyTown, 35
Traceability, 197
Transfer vectors, 199
Transformative operation types, 168
Transformative processes, 89, 168
Transient cavitation, 232
Translations, 3, 12, 41, 98, 100, 104, 109, 138, 157, 178
Transmissible spongiform encephalopathies, 101
Transponder network, 49, 51
Transporter subsystem, 80
Treatise on Man, 1
Treder, Mike, 144
Tree hyrax, 220
Tree shrew, 220
Tribbles, 187
Trinity College, xix
Triple crossover, 92
Trivial self-reproduction, 4
TRIX, 35
tRNA, 97-100, 107, 109, 110, 113
tRNA recognition, 99, 110
tRNA synthetase, 97, 98, 100, 107, 109, 113
Trojan horse, 12, 205
Trumodel, 35
Trypanosomes, 157
TSEs, 101
Tulipa, 156
Tullbery, Sten-Ove, 73
Tumor Amplified Protein Expression Therapy, 109
Tung, Steve, xx, 114
Turberfield, Andrew, 111
Turing automata, 29
Turing gas, 119
Turing machine, 2, 6, 11, 44, 45, 103, 118, 119, 157, 166, 193, 195, 216
Turing patterns, 95
Turner, Linda, 114
Turney, Peter, xx, 14, 15
Two step induction, 163
Typogenetics, 119
Typography of self-reproducer, 157

U

UCLA, 114, 162
Ulam, Stanislaw, 2, 8
Uldrich, Jack, xxi
Ultramicrobacteria, 177
Ultrasonic irradiation, 225
Unexcitable, 8
Unicellular, 69, 103, 163, 174
Unifi Inc., 27
Unilateral disarmament, 204
Unilateral reverse engineering, 16
Unimation, Inc., 46
Unit duplication model, 167
Unit fission model, 167
Unit growth, 46, 49-51, 53, 121, 167
Unit growth model, 167
Unit replication, 46-48, 101, 120, 121, 166, 167, 189, 215
Units of evolution, 172
Unity, xix, xxi, 5, 20, 24, 36, 42, 46, 63, 79, 90, 108, 125, 145, 190, 197, 198, 202, 205, 210, 216, 217
Universal assembler, xvii, 119, 135, 198
Universal bases, 112
Universal construction, 6, 9-12, 108, 180
Universal constructor, 6, 9, 11, 34, 46-48, 63, 79, 156, 170
Universal Telegraph, 209
Universitat Dortmund, xix
Universidad de Granada, xix
Universiteit van Amsterdam (Netherlands), xix
Universities Space Research Association, 78
University College (London), xix, 21, 216
University of Aarhus, xix, 34
University of Aizu, xix

University of Budapest, 5
University of California at Berkeley, xix, 58, 65, 117
University of California at Los Angeles, xix
University of Dortmund, 34
University of Dundee, xix
University of Edinburgh, xix
University of Electro-Communications, xix
University of Florida, xix, 65
University of Guelph, xix
University of Hertfordshire, xix
University of Idaho, xix
University of Illinois, xix, 66
University of Linz, xix
University of Massachusetts, xx, 34
University of Melbourne, xix
University of Minnesota, xix, 33, 117
University of Newcastle upon Tyne, xix
University of New Mexico, xix, 60
University of North Carolina at Chapel Hill, xix
University of North Texas, 140
University of Notre Dame, 44
University of Oxford, 111, 157
University of Pennsylvania, xix, 5
University of Santa Clara, 43
University of Southampton, xix
University of South Carolina, 144, 198
University of Southern California, xix, 65, 89
University of Southern Denmark, xix
University of Sussex, xix
University of Szeged, xix
University of Texas at Austin, xix
University of Texas at Dallas, 140, 144
University of the West of England, xix, 33
University of Tokyo, xix, 182
University of Twente, xix
University of Utah, xix, 116
University of Western Australia, xix
University of Zurich, 34
Unlimited heredity, 148, 149
Unmanned, 26, 27, 36, 43, 78, 184, 208
Unnatural amino acid, 109
Unnatural genetic alphabet, 112
Unnatural nucleobases, 112
Unpowered, 164, 227
Unsafe artificial mechanical replicators, 199
Unsal, Cem, xx
Unsheathed replicating loop, 12
Urban renewal kit, 25
Urdea, M.S., 92
USATU, 117
USC, xviii, xx, 33, 42, 162, 198, 199
USC Information Sciences Institute, xx, 33
U.S. Department of Transportation, 226
U.S. factory manufacturing system, 180
U.S. House Science Committee, 198
U.S. Patent Office, 54, 139, 166
U.S. Patent Office Manual, 166
USRA, 78
USSR Patent Department, 127
Utility fog, 29, 33, 80, 115

V

Vacuum tube, 19, 79
Vaidyanathan, 67
Valdes, Francisco, 188
Vanderbilt University, xix
Van der Waals, 90, 116, 126, 132, 134, 135, 226, 228, 229, 231
Van der Waals adhesion, 135
Van der Waals cage, 134, 135, 226
Van der Waals pegs, 132
Van Nedervelde, Philip, xx, 136
Van Vogt, A.E., 38
Vanuxem lecture, 8, 24
Varela, Francisco J., 145
Varetto, L., 96, 119
Variability, 135, 172, 176
Vaucanson, Jacques de, 1
Vaucanson's duck, 1
Venter, J. Craig, 108
Venture capital, xvii, 175, 204, 216
Verification of production concepts, 184
Vervet, 220
VHDL, 80
vHDV, 102
Vibratory agitation, 151
Vibrio comma, 221
Vicale Corp., 65
Vion Pharmaceuticals, 109
Viral marketing, 13
Virginia Polytechnic Institute, xix
Viroid, 101-103, 110, 156, 221
Viroid-like RNAs, 101
Viroid replication rate, 102
Viroid replication time, 102
Virotherapies, 154
Virtual device, 159
Virtual organisms, 12, 180
Virtual physics, 14
Virtual product, 171
Virtual replicator, 146
Virtual robot, 64
Virus, 1, 12, 89, 94, 101-105, 108, 110, 113-115, 152, 154, 156, 157, 160, 166, 170, 174, 177, 179, 180, 196-199, 204, 205, 208, 219, 221
Virus, computer, 12, 157, 196, 205
Viscous regime, 226, 229, 231
Visual Basic, 184
Visual C^{++}, 184
Vitamin architecture, 107, 138, 153, 161, 170, 196, 199
Vitamin architecture for materials, 196, 199
Vitamin C, 90, 181
Vitamin molecules, 133, 224, 225, 231
Vitamin parts, 107, 153, 161, 162, 181
Vitamin processes, 166
Vitanyi, P.M.B., 172
VLSI Hardware Description Language, 80
Vogel, Viola, 207
Vogue, 35
Volen Center for Complex Systems, 64
Von Ehr, James, 125, 144, 197
Von Goethe, Johann Wolfgang, 155
Von Kiedrowski, Gunter, xx, 17, 91, 92, 95, 96, 112, 114, 139, 190
Von Leibniz, Gottfried Wilhelm, 2
Von Neumann, John, xviii, 2-11, 13-17, 19, 20, 23-25, 29, 38, 40, 45, 46, 55, 63, 64, 101, 104, 118, 120, 132, 146, 150, 154-156, 170, 178, 179, 184, 201
Von Neumann architecture, 6, 38
Von Neumann machine, 6, 38, 64
Von Neumann probe, 38
Von Tiesenhausen, Georg, xx, 44, 46, 132, 187, 188, 189

Von Tiesenhausen unit replication system, 46-48
Voyage of the Space Beagle, 38
Vulcan's Hammer, 19
Vyssotsky, V.A., 12

W

Wachs, Jason, 73
Wachtershauser, G., 96
Wagner, H., 105
Walking microrobot, 116
Wall stiffness during external acoustic forcing, 233
Wall stiffness during internal mechanical activities, 233, 234
Wall sublimation, 234
Walsh, Peter J., 186, 189
Wang, James C.F., 80, 81, 226
Wang tile, 80, 81
Ward, J., 202
Warehouse, 26, 40, 49, 162, 164, 171, 208
Wasserman, Edel, 94
Waste, xxi, 25, 40, 41, 49, 52, 54, 107, 128, 130, 131, 140, 142, 147, 171, 215, 232
Waste heat, 25, 52, 54, 171, 215, 232
Waste products, 131, 171, 215
Water opossum, 220
Wator, 12
Watson, Richard A., 18
Watson-Crick pairing, 91
Weapon, 12, 154, 169, 204, 205
Weapon systems, 154, 205
Wear, 25, 37, 41, 116, 184, 185, 212
Weather simulations, 11
Weineler, Brian, 72
Weiss, Ron, xx, 114
Wendt, Christopher H., xx, 53, 175, 193, 220
Wengel, Jesper, 93
Wenz, G., 93
West, Geoffrey B., 175
Westberg, H., 66
Western larch, 219
Western Union, 209
Wet/natural, 171
When Harlie Was One, 12
Whitaker, Randall, 145
White ash, 219
White fir, 219
Whitehead Institute, 109
White oak, 219
Whitesides, George W., 90, 95
White spruce, 219
Whole gene synthesis, 108
Wiener, Norbert, 5
Wild water buffalo, 219
Wilke, Claus O., 14
Will, Peter, 183
Willful misuse, 197
Wilson, W.C., 67
Winfree, Erik, 95, 111
Winkless, Nelson B., III, 20
Wisdom/Sagesse, 35
Woese, C.R., 101, 177
Wolbachia, 172
Wolpert, L., 163
Wong, Chris, 73
Woods Hole, 42
Wool, 203
Word processing for DNA, 109
Workcell designs, 184
Workpiece, 25, 40, 41, 52, 56, 57, 120-122, 127, 128, 134, 140, 141, 165, 168, 183, 194, 207, 211, 213
Workplace, 158, 159, 167, 171
WorkSpace, 184
Workspace, 63, 127-129, 142, 162, 164
Worm, 1, 12, 65, 134, 156, 196, 205
Wright brothers, 208, 216
Wu, Vincent, 74

X

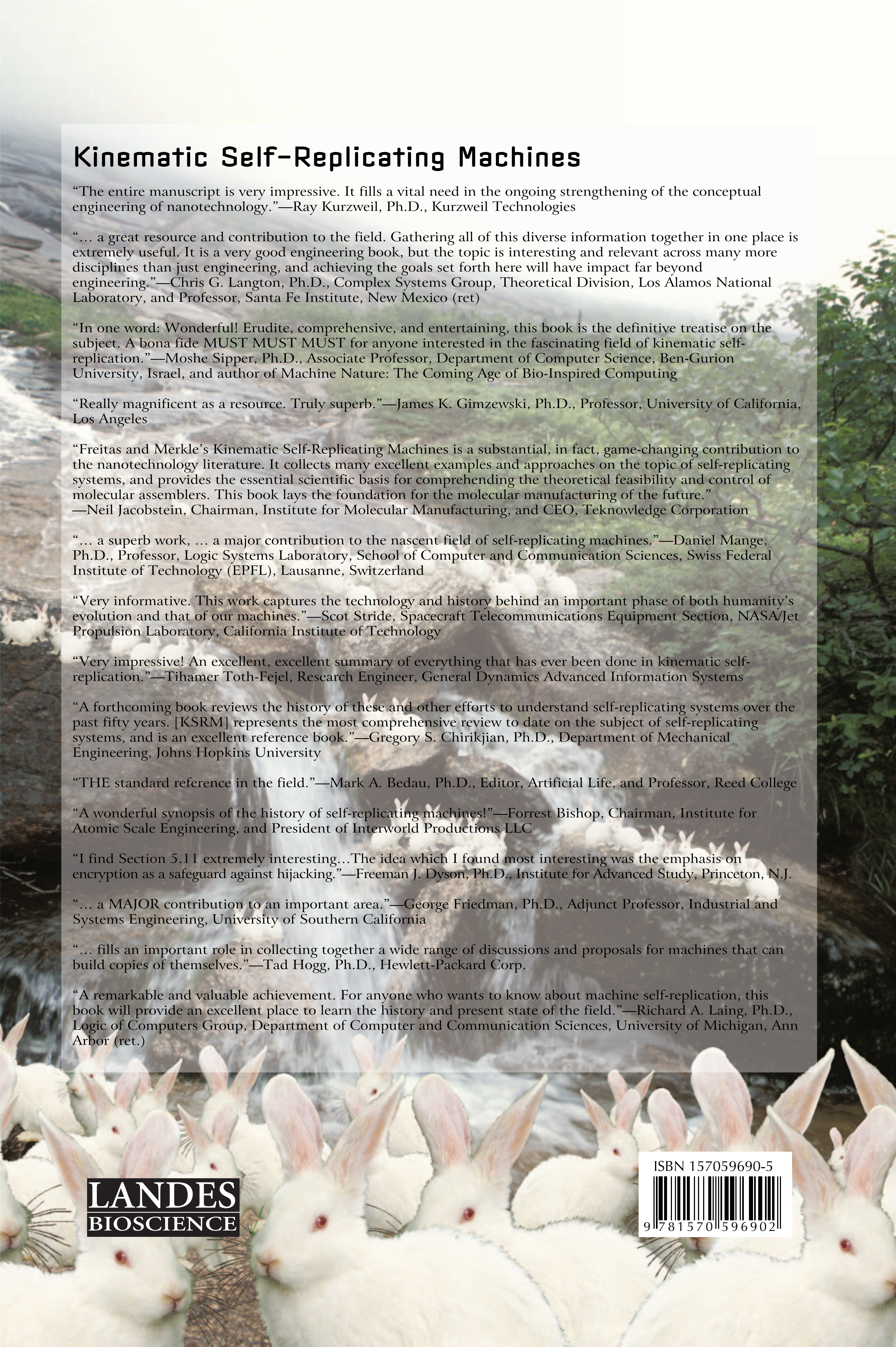
Xenopus laevis, 156
Xerox PARC, xx, 31, 32
Xia, T.K., 231
XOR gates, 125

Y

YACs, 110
Yager, Paul, 228
Yale University, 109
Yamanashi Prefecture, 26, 184
Yamazaki Mazak, 27
Yan, Hao, 112
Yasukawa Electric, 27, 208
Yeast, 96, 109, 110, 113, 156, 166, 199
Yeast artificial chromosomes, 110
Yeh, H.J., 95
Yellow-bellied marmot, 220
Yellow fever, 102
Yim, Mark, xx, 30-32
Yokoyama, Takashi, 91
Yoshida, Eiichi, xx
Young, R.D., 202, 233
Yudasaka, Masako, 225
Yudkowsky, Eliezer S., xx, 154, 169, 172, 173
Yurke, Bernard, xx, 111, 113

Z

Z-3 machine, 209
Zachary, William B., 51
Zama plant, 26
Z Corporation, 66
Zeno's Factory, 138
Zeolite, 93
Zero-emissions, 171
Zero waste, 171
Zettl, A., 212
Zhou, Demin, xx, 102, 110
Zhou, Yu, 69, 71-74
ZigZag, 8, 35
Zipf power law, 176
Zolo, 35
Zome System, 35
Zuse, Konrad, 8, 25, 209
Zygote, 3, 149
Zyvex Corp., xx, 4, 40, 55, 117, 121, 123-126, 128, 129, 135, 136, 138-141, 144, 178, 184, 197, 198, 201
Zyvex exponential assembly, 4, 138
Zyvex microscale assemblers, 144
Zyvex nanomanipulator array assembler system, 135, 136



Kinematic Self-Replicating Machines

"The entire manuscript is very impressive. It fills a vital need in the ongoing strengthening of the conceptual engineering of nanotechnology."—Ray Kurzweil, Ph.D., Kurzweil Technologies

"… a great resource and contribution to the field. Gathering all of this diverse information together in one place is extremely useful. It is a very good engineering book, but the topic is interesting and relevant across many more disciplines than just engineering, and achieving the goals set forth here will have impact far beyond engineering."—Chris G. Langton, Ph.D., Complex Systems Group, Theoretical Division, Los Alamos National Laboratory, and Professor, Santa Fe Institute, New Mexico (ret)

"In one word: Wonderful! Erudite, comprehensive, and entertaining, this book is the definitive treatise on the subject. A bona fide MUST MUST MUST for anyone interested in the fascinating field of kinematic self-replication."—Moshe Sipper, Ph.D., Associate Professor, Department of Computer Science, Ben-Gurion University, Israel, and author of Machine Nature: The Coming Age of Bio-Inspired Computing

"Really magnificent as a resource. Truly superb."—James K. Gimzewski, Ph.D., Professor, University of California, Los Angeles

"Freitas and Merkle's Kinematic Self-Replicating Machines is a substantial, in fact, game-changing contribution to the nanotechnology literature. It collects many excellent examples and approaches on the topic of self-replicating systems, and provides the essential scientific basis for comprehending the theoretical feasibility and control of molecular assemblers. This book lays the foundation for the molecular manufacturing of the future."
—Neil Jacobstein, Chairman, Institute for Molecular Manufacturing, and CEO, Teknowledge Corporation

"… a superb work, … a major contribution to the nascent field of self-replicating machines."—Daniel Mange, Ph.D., Professor, Logic Systems Laboratory, School of Computer and Communication Sciences, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland

"Very informative. This work captures the technology and history behind an important phase of both humanity's evolution and that of our machines."—Scot Stride, Spacecraft Telecommunications Equipment Section, NASA/Jet Propulsion Laboratory, California Institute of Technology

"Very impressive! An excellent, excellent summary of everything that has ever been done in kinematic self-replication."—Tihamer Toth-Fejel, Research Engineer, General Dynamics Advanced Information Systems

"A forthcoming book reviews the history of these and other efforts to understand self-replicating systems over the past fifty years. [KSRM] represents the most comprehensive review to date on the subject of self-replicating systems, and is an excellent reference book."—Gregory S. Chirikjian, Ph.D., Department of Mechanical Engineering, Johns Hopkins University

"THE standard reference in the field."—Mark A. Bedau, Ph.D., Editor, Artificial Life, and Professor, Reed College

"A wonderful synopsis of the history of self-replicating machines!"—Forrest Bishop, Chairman, Institute for Atomic Scale Engineering, and President of Interworld Productions LLC

"I find Section 5.11 extremely interesting…The idea which I found most interesting was the emphasis on encryption as a safeguard against hijacking."—Freeman J. Dyson, Ph.D., Institute for Advanced Study, Princeton, N.J.

"… a MAJOR contribution to an important area."—George Friedman, Ph.D., Adjunct Professor, Industrial and Systems Engineering, University of Southern California

"… fills an important role in collecting together a wide range of discussions and proposals for machines that can build copies of themselves."—Tad Hogg, Ph.D., Hewlett-Packard Corp.

"A remarkable and valuable achievement. For anyone who wants to know about machine self-replication, this book will provide an excellent place to learn the history and present state of the field."—Richard A. Laing, Ph.D., Logic of Computers Group, Department of Computer and Communication Sciences, University of Michigan, Ann Arbor (ret.)

LANDES
BIOSCIENCE

ISBN 157059690-5
9 781570 596902